Coping with Syncope: Tilt Towards Pacing

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Syncope, defined as a transient loss of consciousness and postural tone, is one of the oldest recorded medical problems. The term syncope is derived from the Greek word "synkoptein", meaning "to cut short". One of the most frequently encountered forms of syncope, the vasovagal or the "common faint" is caused by inappropriate reflex vasodilatation and bradycardia and is rarely life threatening. Even in patients, with the so-called "malignant" form of the disease, who have profound cardioinhibition culminating in asystole during tilt tests, no death has been reported on long-term follow-up studies. However, patients with vasovagal syncope are at an increased risk of a fall, which can often result in serious injuries. Those who work as pilots, drivers, etc. can endanger others as well. Patients who develop syncope without enough warning or prodromal symptoms are unable to brace themselves for the usually inevitable “fall”. Thus, patients with syncope have a level of impairment similar to that seen in patients with severe rheumatoid arthritis and psychiatric illness. The quality of life deteriorates as the frequency of syncopal spells increases. Therefore, vasovagal syncope is not “truly benign” and these patients need to be treated. At present, there is no consensus on the management of patients with vasovagal syncope. If syncopal episodes are infrequent, simple nonpharmacologic measures usually suffice. In those with severe symptoms, tilt test-guided therapy or empiric pharmacotherapy is recommended. If drugs fail, permanent pacemakers are advocated. However, this treatment algorithm has to be individualized, taking into consideration age, occupation, symptomatic status and response to head-up tilt test (HUTT).

Non pharmacological Methods

Salt supplementation and increased fluid intake, by increasing the extracellular fluid volume, may reduce the impact of orthostatic blood pooling. These simple measures are commonly recommended as initial therapy. Although large controlled trials are lacking, they have been shown to be of some benefit in small studies.

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Pharmacotherapy

Several pharmacologic agents targeting the afferent limb (fludrocortisone), efferent limb (beta-blockers) or both (midodrine) of this reflex-mediated syndrome have been advocated to manage these cases. Many small, nonrandomized trials have been reported using beta-blockers, clonidine, disopyrimide, angiotensin-converting enzyme inhibitors, dextroamphetamine, etilefrine, fludrocortisone, methylphenidate, midodrine, phenylephrine, propan-theline, scopolamine, serotonine-reuptake inhibitors and theophylline. However, as the natural history of this disease entity can be variable, critical assessment of the efficacy of any pharmacologic agent requires a randomized clinical trial.

Beta-blockers: These are the most widely prescribed drugs in clinically encountered vasovagal syncope, often as empiric therapy. They presumably act by inhibiting the activation of ventricular mechanoreceptors and by blocking the effects of surging catecholamines in the circulation. Despite extensive clinical experience with the drug, there is a dearth of controlled studies. Several nonrandomized studies have demonstrated its clinical efficacy with recurrence rate reduced to 6%-28% with treatment. In a large study by Cox et al., 296 consecutive patients were put on tilt-guided or empiric beta-blocker therapy. During a follow-up of 28±11 months, 90% of patients on tilt-
guided beta-blocker therapy remained symptom-free compared with 77% on empiric therapy. Similar results were reported in another large nonrandomized study by Natale et al. They demonstrated a 6% recurrence rate of symptoms on tilt-guided beta-blocker therapy among 210 patients, while the recurrence rate was 36% when empiric beta-blocker therapy was given.

Only two randomized, placebo-controlled trials have been published. In the first double-blind, randomized, placebo-controlled study by Mahanonda et al., 42 patients with a positive tilt test were randomized to atenolol or placebo. They were subjected to a repeat tilt test after one month. The response rates (negative HUTT) were 62% v. 5% (p=0.0004) for the atenolol and control groups, respectively. Moreover, 71% patients reported a subjective sense of well-being in the atenolol group compared with 29% in the placebo group (p=0.02). The frequency of syncopal attacks reduced from 6.0+9.4 per week to 0.6+1.6 per week in the atenolol group (p=0.025). This was the first controlled trial demonstrating the benefit of beta-blockers. However, many a question regarding the long-term efficacy of the drug, its tolerability and side-effects remained unanswered due to the short follow-up of only one month.

The second study was published 6 years after the earlier trial. In this prospective, double-blind, randomized and placebo-controlled study, 50 patients with syncope, of whom 20 (40%) had an abnormal tilt test, were randomized to atenolol or placebo. During the one year of follow-up, 16 patients on atenolol and 11 patients on placebo had recurrence of syncope (61% v. 45%, p=0.09). The authors concluded that beta-blockers were no more beneficial than placebo. However, only 20 patients (40%) in this study had an abnormal response to tilt testing at baseline. Previous studies, including the favourable study by Mahanonda et al., included only patients with a positive tilt test in the trial. The difference in the inclusion criteria in the two studies may have had a significant impact on the results obtained. It is indeed surprising that the investigators assigned even patients with a negative tilt test (steep angle of 80° for 45 min) to the trial. There are no prior studies in the literature showing the efficacy of elective beta-blocker therapy in patients with presumed neurocardiogenic syncope. The fact that only 5 patients included in this study had responded favorably to intravenous atenolol may also be responsible for the reported high incidence of recurrence. Previous studies have demonstrated that patients who respond to intravenous beta-blockers during tilt testing, also have a favorable response to oral beta-blockers on long-term follow-up. In the study by Sra et al., all patients with a negative tilt test during esmolol infusion also had a negative tilt response with oral metoprolol. Of the patients with a positive tilt test during esmolol infusion, 90% continued to have a similar response with oral therapy. Because only 5 patients (25%) had responded favorably to intravenous atenolol in the study by Madrid et al., it is not surprising that the response to oral atenolol was correspondingly poor. Although the authors had questioned the efficacy of beta-blockers in vasovagal syncope, the conclusions of the study need to be re-examined and interpreted critically.

It appears that beta-blockers are effective in the treatment of patients with vasovagal syncope; however, further scrutiny is needed in large randomized trials with appropriate numbers and extended follow-up. For now, beta-blockers retain their hallowed place as the first line of treatment for vasovagal syncope. Other medications should be used if the patient does not respond or does not tolerate beta-blockers because of side-effects such as bradycardia, impotence, bronchospasm or AV blocks.

**Fludrocortisone:** There is a wealth of clinical experience with fludrocortisone. Though controlled studies are lacking, it is commonly used to treat vasovagal syncope, especially in children. Fludrocortisone is a mineralocorticoid that acts by increasing the renal absorption of sodium, thereby expanding the blood volume. It may also affect the baroreceptor sensitivity and enhance the effects of circulating catecholamines by increasing the sensitivity of blood vessels to their vasoconstrictive effects.

In a study by Scott et al., 58 pediatric patients were randomized to receive atenolol or fludrocortisone acetate. At the end of 6 months, 48 patients (83%) showed clinical improvement (no recurrence or significant decrease in frequency/severity of episodes). Both drugs were equally effective. Neither the response to intravenous beta-blockers, nor the presence of tachycardia was predictive of long-term response to oral beta-blockers. This is contrary to earlier studies in which a positive response to intravenous beta-blockers predicted a favorable long-term response to oral beta-blockers. Similarly, the presence of tachycardia during the tilt test had predicted a favorable response to oral beta-blocker therapy in an earlier study by Leor et al. In a study involving 21 children who were treated with fludrocortisone, 20 experienced no recurrences of syncope on follow-up for 20 months. Although small nonrandomized studies have demonstrated the usefulness of this drug, no randomized, placebo-controlled trial has been published. Despite this, fludrocortisone continues to be a popular choice amongst clinicians because of its patient-friendly profile and minimal side-effects (hypertension, edema, acne, depression and rarely, hypokalemia).
**Alpha-adrenergic agonists:** These agents increase the venous tone, thereby reducing venous pooling and thus possibly the paradoxical activation of cardioreceptors. The increase they cause in arteriolar tone may counterbalance the reflex vasodilatation and hypotension that culminate in overt syncope.

Though the initial trials showed promise, they were open-label studies with a small number of patients and used different drugs such as phenylephrine,25 methylphenidate,26 and dextroamphetamine.27 Only midodrine has proved to be of use in a randomized, placebo-controlled trial.28 Ward et al.,29 randomized 16 patients to midodrine or placebo and reported significant improvement in the frequency and recurrence of symptoms. Also, the quality of life improved significantly in the patients on midodrine. In another study with midodrine,30 11 patients were followed up for a mean of 4.3 months. There was a significant clinical improvement in 9 patients with complete resolution of symptoms in 5 of them.

Small, nonrandomized trials had also found etilefrine, another alpha-adrenergic agonist, to be beneficial. However, recently a double-blind, randomized, placebo-controlled trial with etilefrine failed to confirm its efficacy.30 Both the treatment and placebo arms (63 patients in each) had the same recurrence rate of syncope (24%). The median time to the first syncope (106 v 112 days) and the incidence and number of presyncopal episodes were also not significantly different. This well-crafted VASIS study30 has put a question mark on the usefulness of alpha-adrenergic agonists in vasovagal syncope. Despite the initial promise, large randomized trials are needed to further the claims of midodrine as an agent that can be relied upon in this condition.

**Serotonin-reuptake inhibitors:** Serotonin is a neurotransmitter which mediates the development of hypotension and bradycardia, both of which are essential components of vasovagal syncope. Therefore, serotonin-reuptake inhibitors such as paroxetine, fluoxetine and sertraline could be of value in the treatment of this entity. Grubb et al.31 anecdotally observed that treating patients who suffered from endogenous depression as well as neurocardiogenic syncope with fluoxetine resulted in the resolution of their clinical syncope. This observation paved the way for clinical trials with this class of drugs. In their study, 16 patients with resistant vasovagal syncope and a positive tilt test were treated with fluoxetine and restudied 5–6 weeks later. Of the 13 patients (3 could not tolerate the drug) 7 (53%) were rendered tilt test negative and remained asymptomatic over a mean follow-up of 19±9 months.

Di Girolamo et al.32 studied the effects of paroxetine hydrochloride on vasovagal syncope in a randomized, double-blind, placebo-controlled trial. The response rates (negative HUTT after 1 month) were 61.8% and 38.2% in the paroxetine and placebo groups, respectively. During the follow-up of 25.4±8 months, recurrence of syncope was seen in 17.6% in the paroxetine group as compared to 52.9% in the placebo group (p<0.0001). Only 1 patient (2.9%) discontinued the drug due to severe headache. This is a significant study; it being a placebo-controlled, randomized trial showing evidence of improvement.

Sertraline has also been found to be effective in children with vasovagal syncope in small nonrandomized trials.33,34 Incapacitating side-effects such as anxiety, insomnia, drowsiness, anorexia and fatigue restrict the use of serotonin receptor antagonists.

**Disopyramide:** This class IA antiarrhythmic agent has a negative inotropic, anticholinergic and a direct peripheral vasoconstrictive effect which theoretically makes it an ideal drug to combat syncope. Small, nonrandomized studies have shown disopyramide to be beneficial. In a study by Milstein et al.,35 a repeat tilt test after oral disopyramide therapy for 3 days was performed in 10 patients. All of them had a negative test and during a subsequent follow-up after 20±5 months, all but one patient remained asymptomatic. In another study,36 of the 6 nonresponders to beta-blocker therapy, subsequently treated with disopyramide, only 1 had recurrence of syncope in the follow-up period of 9±3 months. In a double-blind, randomized trial, Morillo et al.36 studied 22 patients who were serially tilt tested with intravenous and then oral disopyramide. Neither form of disopyramide was found to be superior to placebo in preventing tilt-induced or spontaneous syncope. During follow-up of 29±8 months, syncope recurred in 27% of patients on drug therapy compared to 30% on placebo. Because of the potential for pro-arrhythmias and the presence of significant anticholinergic effects, disopyramide is not considered as first-line therapy for vasovagal syncope.

**Other pharmacologic agents:** Anticholinergic agents might be effective by reducing the high vagal tone that occurs during vasovagal syncope. Small numbers of patients were successfully treated with transdermal scopolamine in a few nonrandomized studies.19,37 However, Lee et al.38 found no benefit of the drug over placebo in a randomized trial of 60 patients.

Theophylline blocks the action of adenosine which is a mediator of hypotension and bradycardia. However, two small, nonrandomized studies19,40 have demonstrated conflicting results with the drug.
Oral enalapril, an angiotensin-converting enzyme inhibitor, has also shown promise in 30 patients with vasovagal syncope in a randomized, double-blind, placebo-controlled trial. All the 15 patients given enalapril had a negative repeat tilt test. During a follow-up of 13.4±2.1 months, 14/15 (93%) patients on enalapril remained symptom-free compared with 3/15 in the placebo group. Further studies are required to assess the full potential of this class of drugs in treating patients with vasovagal syncope.

Role of tilt testing in guiding pharmacotherapy: Tilt test-guided therapy has generally been found to be more effective than empiric treatment. In a study of 303 patients, 44 received empiric therapy, 210 were treated with tilt test-guided medications, and 49 refused treatment. Of the 210 patients on tilt test-guided therapy, 130 were on beta-blockers, 35 on theophylline, 10 on ephedrine, 31 on disopyramide and 4 on combination therapy. Empiric therapy consisted of beta-blockers in most of the patients. Recurrence of symptoms was seen in only 6% of the patients on tilt test-guided therapy compared with 36% on empiric therapy and 67% in no treatment group.

Conclusions: Although several pharmacologic agents have been used for the treatment of vasovagal syncope, there is a remarkable absence of scientific proof of their efficacy from large, prospective, randomized clinical trials. In fact, only three agents have shown to be of benefit in randomized clinical trials—atenolol, midodrine and paroxitene. Beta-blockers are still the old favorite as the other two have significant side-effects. However, the only two randomized trials available on their efficacy have yielded conflicting results. Of late, clinicians have realized the need of looking beyond beta-blockers, and have started considering other treatment options.

Pacing for Vasovagal Syncope

The need for a therapy beyond drugs was felt when drug-resistant fainters with “malignant syncope” were encountered. These patients form a high risk for “falls with the faint” and have a severely restricted lifestyle with significant physical and psychosocial handicap. The bradycardia or asystole component of the vasovagal syncope which along with hypotension culminates in the clinical cascade, theoretically makes pacing support during the episode seem the final answer to this vexing problem.

In earlier studies, vasovagal syncope induced by tilt testing was used as a model for clinical syncope, to determine whether pacing could be helpful. In these studies, patients who had a positive tilt test with marked bradycardia underwent a second tilt test with temporary pacing at rates of 85–100 beats/min. Fitzpatrick et al. using temporary dual-chamber pacing with rate hysteresis could prevent syncope in 5 out of 7 patients. In these 5 cases, syncope was prevented despite the onset of a vasovagal reaction attested to by fall in blood pressure and the development of sufficient bradycardia to initiate pacing. Similarly, Samoil et al. reported prevention of syncope in 3 out of 6 patients with pacing. In the study by Sra et al., 22 patients with bradycardia or asystole along with hypotension during tilt testing underwent a second tilt-test with dual-chamber temporary pacing at a rate of 20 beats/min above their resting rate. They found that 15 patients still had presyncope and 5 patients went on to have frank syncope during pacing. Although the authors felt that pacing was not useful in vasovagal syncope, a shift from syncope at baseline in 18 patients to syncope in just 5 patients during pacing represents a significant clinical improvement as far as frank syncope is concerned. The results were similar to the earlier study by Fitzpatrick et al., in which the authors had concluded that modification of the vasovagal episode during temporary pacing could translate into a clinical advantage with permanent pacing. Overall, temporary pacing was shown to prevent syncope in more than half the patients.

The initial studies with permanent pacing were historically controlled. Peterson et al. reported their experience of 37 patients with vasovagal syncope who were implanted dual-chamber pacemakers with rate hysteresis. These pulse generators had sensors that detected the fall in heart rate to 40–50 beats/min and responded with pacing rates of 80–90 beats/min. During the follow-up of 39±19 months, 89% of patients reported symptomatic improvement and 62% had no recurrence of syncope.

A similar benefit was reported using a permanent dual-chamber rate-drop response pacing algorithm by Benditt et al. With this feature, the pacemaker can be programmed to detect a small rapid drop of heart rate and then pace at a relatively high rate to provide chronotropic support during the time of presumed vasodilatation. All the parameters, i.e. the lowest rate, top rate and the time period are programmable. During an average follow-up of 6 months, syncope was prevented in 78% of cases.

A third type of pulse generator with automatic rate-drop sensing mode was tested by Sheldon et al. In this, the dual-chamber pacemaker senses if the sensed heart rate drops by >15 beats/min/beat. The initial pacing rate is 15 beats/min below the rate preceding the rate decrease, and then slowly decreases at 0.5 beats/min/beat until the intrinsic heart rate exceeds it. With this “rate slow-smoothing” pacing algorithm,
the frequency of syncope was reduced by 93% and 50% had no recurrence. The median time to syncope recurrence before and after pacing was 7 days and 5.3 months, respectively. There was also a marked improvement in the quality of life.

Thus, irrespective of the algorithm used, benefit was demonstrated in these nonrandomized studies with permanent dual-chamber pacing, and the results were comparable. A recent study has now confirmed the benefit of dual-chamber pacing over single-chamber ventricular pacing. However, as these trials were historically controlled, the next step was to demonstrate the benefit in controlled studies.

**Randomized pacemaker trials:** There are only a few controlled trials available to study the efficacy of pacing in vasovagal syncope.

The North American Vasovagal Pacemaker Study (VPS-I) was the first randomized trial to show benefit with permanent pacing. In this trial, 54 patients with more than six lifetime episodes of syncope and a positive HUTT (with syncope or presyncope and relative bradycardia), were randomized to dual-chamber pacing with rate-drop response and no pacing. Patients in both the groups were permitted to receive medical treatment according to the judgment of treating physician. It was found that syncope recurred in 19/27 (70%) patients who did not receive pacemaker compared to 6/27 (22%) in the pacemaker group, showing a 85.4% relative risk reduction. However, there was no difference in the occurrence of presyncope, with at least one episode of presyncope reported by 74% of the no pacemaker group and 63% of the pacemaker group. The mean time from randomization to syncope also increased in the pacemaker group (112 days) compared to no pacemaker group (54 days). However, it was an open-label study, therefore a placebo-type effect or psychological benefit from receiving a pacemaker cannot be excluded. Also, there was no standardization of medical therapy in the study. At the end of the study, it was not clear whether the conventional bradycardia support benefited the patients or the rate-drop response algorithm. This particular aspect would become clear after publication of the results of the VPS-II trial, comparing the effectiveness of DDD pacing with and without the rate-drop response, which is currently in progress.

The Vasovagal Syncope International Study (VASIS) investigators showed that plain DDI pacing with rate hysteresis reduced the likelihood of syncope in a select high-risk group. They included 42 patients who had at least three syncopal episodes in the preceding two years with a positive cardioinhibitory response to HUTT. Nineteen patients received DDI pacemakers programmed to 80 beats/min with rate hysteresis of 45 beats/min and 23 received no pacemaker. No drugs were prescribed in either group. There was recurrent syncope in 14/23 (61%) patients after a median time of 5 months in the no pacemaker group versus 1/19 (5%) in the pacemaker group (after 15 months) (p<0.0006). This benefit was maintained over a long period (mean follow-up 3.7±2.2 years). The Kaplan–Meier actuarial estimates of the first recurrence of syncope after 1, 3 and 5 years were 0%, 6% and 6% in the pacemaker group and 39%, 50% and 75% in no pacemaker group, respectively. There was recurrence in only 5%, a rate much lower than previous studies, including VPS-I. In this trial, the highest-risk category patients with a severe cardioinhibitory response to the tilt test were selected - 79% of pacemaker-treated patients and 91% of controls had an asystolic response during HUTT. Thus, in this study, patients with a more severe cardioinhibition were included, compared with the VPS-I study, in which only one-third of patients developed a heart rate of less than 40 beats/min at baseline tilt test. Like the previous VPS trial, the placebo effect cannot be excluded as the control group did not include implantation of a device. Recurrences of presyncope and dizziness were not studied.

Ammirati et al. recently published the first randomized, controlled trial comparing the effect of medical treatment with pacemaker therapy (DDD with rate-drop response) in patients with recurrent vasovagal syncope. The inclusion criteria were similar to those of the VASIS study. Of the 93 patients randomized, 46 received a DDD pacemaker with rate-drop response. The other 47 patients were given atenolol 100 mg/day. There was a recurrence in 2/46 (4.3%) patients in the pacemaker group after a median time of 390 days as compared with 12/47 (25.5%) patients on atenolol therapy after a median of 135 days (p=0.004). Pacemaker therapy was associated with 93% actuarial probability of remaining free of syncopal recurrence after 3 years, whereas in the medically treated group, the probability was reduced to only less than 67% for the same period of time. This study was not blinded and there was a bias towards giving the pacemaker option to older, highly symptomatic patients. Data on presyncope were not collected. Although 26% of patients in the atenolol group reported side-effects, only one patient discontinued therapy.

In a small study of 12 severely symptomatic children, McLeod et al. performed a three-way, double-blind, randomized, crossover study in which the pacemakers were programmed to sensing only (no pacing), single-chamber ventricular pacing with rate hysteresis or dual-chamber pacing with rate-drop response for 4-month periods, with
each patient randomized to one of the 6 possible orders of the 3 pacing modes. They found that both VVI and DDD pacing significantly reduced the episodes of syncope compared with no pacing (p=0.0078). This proved the beneficial role of pacing over and above any possible placebo effect. VVI and DDD pacing were comparable in terms of reducing syncope but the dual-pacing mode was superior when pre-syncopal was also considered (p=0.039).

These trials included only a highly selected group of “fainters”—high frequency of syncopal attacks, severe cardioinhibition with asystole or syncope during HUTT. Clinical improvement has been demonstrated in all the randomized studies. However, how much of this benefit is because of the psychological impact of a surgical procedure imparting a placebo effect has to be further looked into. In the VPS-I study, there was an absence of any reduction in the frequency of presyncopal attacks in the paced patients. The investigators used this negative point to eliminate any concerns regarding placebo effect, arguing that if placebo effect could decrease the incidence of syncope, it should also reduce the frequency of episodes of presyncope or lightheadedness. The study by McLeod et al. is the only one so far that has demonstrated the superiority of pacing over no pacing. However, this was only a small study involving 12 children with documented asystole of >4 s.

Selection of patients: Almost all trials have used tilt testing to identify patients who would benefit from permanent pacing. But the hypothesis on which this selection is based, i.e. the greater the cardioinhibition, the more the likelihood of pacing therapy being effective, has yet to be confirmed. Follow-up studies of asystolic responders on tilt testing did not reveal a more malignant outcome. In the study by Peterson et al. on pacing, patients with an asystolic response during tilt testing fared no better than those with less severe cardioinhibition. It is also uncertain whether bradycardia during tilt testing automatically translates into bradycardia during clinical syncope. Whether a negative test on temporary pacing can predict a long-term favorable effect on permanent pacemaker is also not proved. In the VASIS study, the long-term efficacy of a permanent pacemaker was clearly demonstrated despite repeat tilt testing at 15 days showing no benefit of pacing over placebo (the positive response on tilt test being 59% and 61%, respectively). Similarly, in the study by Sheldon et al., the outcome of the tilt test did not have any bearing on whether patients had recurrence of syncope after pacemaker insertion. One of the 2 patients with negative tilt test results had a recurrence, compared to 5 of 10 patients with positive test results.

The higher frequency of syncopal episodes has also been shown to be predictive of a greater probability of syncopal relapse. However, in all the randomized trials, there was a low recurrence rate despite the predicted high risk of relapse in the highly symptomatic study population. For example, in the control arm of the VASIS study, there was a recurrence rate of 0.44% per year during a follow-up of more than 3 years. Because this was lower than in the 2 years preceding enrollment, there was an obvious spontaneous decrease in the syncopal episodes even in the absence of any active or placebo treatment. The cyclic course of vasovagal syncope, the possible therapeutic effect of tilt training and patient education are confounding factors that may be responsible for the observation. Patients who are older and have a history of traumatic falls are often considered likely candidates for permanent pacing. However, logical as it seems, there is no data to substantiate this. At present, tilt testing and clinical presentation are relied upon to select patients for pacing; the future may lie in implantable loop recorders that would correctly identify the cardiac event responsible.

Type of pacing: The pacemakers used to treat vasovagal syncope detect decrease in heart rate as the sensed event in 1 of the 3 options. All the three sensing modes—rate-drop response, rate smoothing, and rate hysteresis—have demonstrated comparable benefit with both temporary and permanent pacing. No large study comparing these different modes is available. Future trials such as VPS-II might show the superiority of one specialized pacing algorithm over the other.

Ideal end-point: One of the important issues is to establish a consensus for assessing the efficacy of treatment in vasovagal syncope. Syncope is known to occur in clusters with long, symptom-free intervals. Therefore, recurrence of syncope is not an ideal end-point to establish efficacy. Other end-points such as time to first recurrence, asymptomatic intervals and overall syncopal burden over a period of time should also be considered.

Conclusions: Does the demonstrable benefit in three successive randomized trials mean lowering of the threshold for permanent pacing in vasovagal syncope? At present, cautious optimism would be advisable. A careful assessment of the clinical profile, the physical, psychological and social handicap, and other factors such as occupational necessity is required. Tilt testing remains the only test that one turns to, despite its limitations. In future, implantable loop recorders would probably prove to be more useful. Larger, multicenter studies with longer follow-up are needed to resolve many unanswered questions.
symptomatic patients who are resistant to drugs and who are particularly prone to injuries or accidents.

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New Techniques for Mapping Cardiac Arrhythmias

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Essential to the effective management of any cardiac arrhythmia is a thorough understanding of the mechanisms of its initiation and sustenance.1–13 Conventionally, this has been achieved by careful study of the surface electrocardiogram (ECG) and correlation of the changes therein with data from intracavitary electrograms picked up by catheters which were maneuvered to lie in contact with the endocardium in various key locations within the cardiac chambers. A record of these electrograms documenting multiple sites simultaneously is studied to deduce the mechanisms of an arrhythmic event. However, these methods do not cover a vast area of the endocardial surface. Painstaking spot-by-spot maneuvering of the catheter is required to trace the origin of an arrhythmic event and its activation sequence in the neighboring areas. To obtain a more accurate picture of the spread of activation in all directions from the origin of the arrhythmia would require covering every possible area of the endocardium with an electrogram-recording catheter. Conventional mapping techniques thus have significant limitations. Using current techniques it is difficult to conceive the three-dimensional (3-D) orientation of cardiac structures as these use a limited number of recording electrodes guided by fluoroscopy. Although catheters using multiple electrodes to acquire data points are available, the exact location of an acquired unit of electrophysiological data is difficult to ascertain due to inaccurate delineation of the location of anatomic structures. The laborious process of precise mapping with conventional techniques exposes the electrophysiologist, staff and patient to undesirable levels of radiation from the extended fluoroscopy time. Another drawback of conventional techniques is the inability to identify several sites and then return to the most appropriate or optimal site. This inability to identify, for example, the site of a previous ablation increases the risk of repeated ablation of areas already dealt with and the likelihood that new sites may be missed. The ability to identify the position of the ablation catheter within a 3-D model where the sites are tagged would thus help to avoid ablation of unwanted areas and minimize the use of fluoroscopy. Although several mapping techniques have been developed in the last few years, electroanatomic (commonly called “CARTO”) and noncontact mapping are most commonly used. The purpose of this report is to give a comprehensive description of these techniques and their use in the treatment of some key arrhythmias.

Electroanatomic Mapping

Electroanatomic or CARTO mapping is a nonfluoroscopic mapping system which uses a special catheter to generate 3-D electroanatomic maps of the heart chambers.13–39 This system uses magnetic technology to accurately determine the location and orientation of the mapping and ablation catheter while simultaneously recording local electrograms from the catheter tip. By sampling electrical and spatial information from different endocardial sites, the 3-D geometry of the mapped chamber is reconstructed in real-time and analyzed to assess the mechanism of arrhythmia and the site appropriate for ablation.

Fundamentals of electroanatomic mapping and the mapping system: Electroanatomic mapping is based on the premise that a metal coil generates an electrical current when placed in a magnetic field. The magnitude of the current depends on the strength of the magnetic field and the orientation of the coil in it. The CARTO mapping system consists of an ultralow magnetic field emitter, a location sensor inside the mapping and ablation catheter tip, a data processing unit and a graphical display unit to generate the electroanatomic model of the chamber being mapped. The magnetic field emitter, mounted under the operating table, consists of three coils which generate a low-intensity magnetic field, around 0.05–0.2 Gauss. In comparison the magnetic field inside a magnetic resonance imaging (MRI) machine is approximately 150–250 000 Gauss. In comparison the magnetic field inside a magnetic resonance imaging (MRI) machine is approximately 150–250 000 Gauss. The mapping and ablation catheter tip is similar to the routine ablation catheter. It is a 7 F quadripolar, deflectable, steerable catheter and can be easily manipulated inside the heart.

The data of the amplitude, frequency and phase of the magnetic field are gathered and analyzed by the processing unit and displayed on the display unit. The CARTO mapping system uses a triangulation algorithm similar to the Global...
Positioning System (GPS). The sensor in the catheter tip detects the intensity of magnetic field generated by each coil, allowing for determination of its distance from each coil. These distances determine the area of theoretical spheres around each coil (Fig. 1) and the intersection between these spheres determines the location of the tip of the catheter. The accuracy of determination of the location is highest in the center of the magnetic field; therefore, it is important to position the location pad under the patient’s chest.

In addition to the x, y and z coordinates of the catheter tip, the CARTO mapping system can determine three orientation determinants—roll, yaw and pitch (Fig. 1). The position and orientation of the catheter tip can be seen on the screen and monitored in real-time as it moves within the electroanatomic model of the chamber mapped. The catheter icon has four color bars (green, red, yellow and blue) enabling the operator to view the catheter as it turns clockwise or counterclockwise (Fig. 2). In addition, since the catheter always deflects in the same direction, each catheter will always deflect towards a single color. Hence, to deflect the catheter to a specific wall, the operator should first turn the catheter so that this color faces the desired wall.

Important aspects of mapping: Several critical elements need to be defined before appropriate arrhythmia mapping can be performed (Fig. 3). As CARTO mapping is not an imaging technique, fluoroscopy is initially used for orientation by taking known anatomic locations in the heart as references to create the model of the mapped chamber.

When mapping the heart the system may deal with four types of motion artifacts:
(i) cardiac motion—the heart is in constant motion; thus the location of the mapping catheter changes throughout the cardiac cycle;
(ii) patient motion;
(iii) respiratory motion—intrathoracic change in the position of the heart during the respiratory cycle; and
(iv) system motion.
Several steps are taken by the CARTO mapping system to compensate for these possible motion artifacts and to ensure that the initial map coordinates are appropriate.
First, a reference signal called the reference electrogram is selected. This is the fiducial marker on which the entire mapping procedure is based. The location of the catheter is gated to a fiducial point in the cardiac cycle which is determined only once per cardiac cycle. In building a 3-D map, both the anatomic location and the electrogram at the anatomic point are acquired by the mapping catheter, which is moving from point to point. The timing of the fiducial point is used to determine the activation timing in the mapping catheter in relation to the acquired points and to ensure collection of data during the same part of the cardiac cycle and is, therefore, vital to the performance of the system. The fiducial point is defined by the user by assigning a reference channel and an annotation criterion. The timing of all electrophysiologic information displayed on the completed 3-D map is relative to the fiducial point. As depicted in Fig. 3 during an accessory pathway mapping surface ECG lead is selected with maximum dV/dt being the fiducial point. All of the local activation timing information recorded by the mapping catheter at different anatomic locations during mapping will be relative to this fiducial point.
point, with the acquisition being gated so that each point is acquired during the same part of the cardiac electrical signal. It is important that the rhythm being mapped is monomorphic and the fiducial point is reproducible at each sampled site. The system has a great deal of flexibility in terms of choosing the reference electrogram, fiducial point and gating locations. Any ECG lead or intracardiac electrogram in bipolar or unipolar mode may serve as a reference electrogram. For the purpose of stability when intracardiac electrograms are selected, coronary sinus electrograms are usually chosen. The fiducial point of the reference electrogram may be the maximum or minimum slope.

The second important concept is that of an anatomic reference. Once the mapping catheter is placed inside the heart, its location in relation to the fixed magnetic field sensors placed under the patient can be determined. Thus, if the mapping catheter moves from one location to another, the CARTO mapping system tracks the location. However, several of the factors mentioned earlier, including a change in the patient's position during the procedure, can result in loss of orientation of the structures. To overcome the effect of motion artifacts, a reference catheter with a sensor similar to the mapping catheter is used. This reference catheter is fixed in its location inside the heart or on the body surface. When the patient moves, this anatomic reference sensor moves with the patient. The CARTO mapping system continuously calculates the position of the mapping catheter in relation to the anatomic reference, thus solving the problem of any possible motion artifacts.

The intracardiac reference catheter has the advantage of moving with the patient's body and with the heart during the phases of respiration. However, the intracardiac reference catheter may change its position during the course of the procedure, especially during manipulation of the other catheters. It is therefore better to use an externally positioned reference catheter strapped to the back of the patient's chest in the interscapular area. The movement of the ablation catheter is then tracked relative to the position of this reference catheter.

The next most important aspect in ensuring the accuracy of the initial map coordinates is to define a window of interest (WOI). This is defined as the time interval relative to the fiducial point, during which the local activation time (LAT) is determined. The total length of the WOI should not exceed 90% of the cycle length of the tachycardia and is usually 90% of the cycle length of the tachycardia. The boundaries are set relative to the reference electrogram. Thus, as depicted in Figs 3 and 4, the window is defined by two intervals, one extending before the reference potential and the other after it.

The final important concept in CARTO mapping is the determination of local activation time or LAT. Once the reference electrograms, anatomic reference and WOI have been preset by the user, the CARTO system will automatically measure timing intervals inside the WOI and ignore events occurring outside it. This allows the user to include or exclude electrical signals, and facilitates the acquisition of detailed, meaningful maps. From: Gepstein et al. Electroanatomical mapping of the heart: basic concepts and implications for the treatment of cardiac arrhythmias. Pacing Clin Electrophysiol 1998; 21: 1271. Reproduced by permission.

The second important concept is that of an anatomic reference. Once the mapping catheter is placed inside the heart, its location in relation to the fixed magnetic field sensors placed under the patient can be determined. Thus, if the mapping catheter moves from one location to another,
been chosen, the mapping catheter is moved from point to point. These points can be acquired in a unipolar or bipolar model. Unipolar recordings have the advantage of providing a more precise measurement of LATs because the steepest negative intrinsic deflection (minimum dV/dt, minimum slope) correlates well with maximal Na⁺ conductance. However, in areas of scar tissue, unipolar recordings may suffer from poor signal-to-noise ratio. In this case, it may be preferable to use the bipolar signal as it may reduce the far-field effect, although the local activation is less precisely defined.

The LAT at each sampled site is calculated as the time interval between the fiducial point on the reference electrogram and the corresponding local activation determined from the unipolar or bipolar local electrogram recorded from that site.

**Electroanatomic mapping procedure:** Following selection of the reference electrogram, positioning of the anatomic reference and determination of the WOI, the mapping catheter is positioned in the mapping chamber under fluoroscopic guidance. The catheter is initially positioned at known anatomic points that serve as landmarks for the electroanatomic map. For example, to map the right atrium, points such as the superior vena cava, inferior vena cava (IVC), bundle of His and the ostium of the coronary sinus are marked. The catheter tip is then advanced slowly along the different walls. Analysis of the anatomic position of these points and the electrograms obtained from them generate real-time 3-D models on a monitor display. The selected points are connected by lines to form several adjoining triangles (Fig. 5) in a global model of the chamber that can be easily rotated to any degree, including standard views. Next, gated electrograms are used to create an activation map which is superimposed on the anatomic model.

To create the activation map, points are color-coded (red for the earliest electrical activation areas; orange, yellow, green, blue and purple for progressively delayed activation areas). Between these points, colors are interpolated and the adjoining triangles are colored with these interpolated values. However, if the points are widely apart, no interpolation is done. The degree to which the system will interpolate activation times is programmable (as the triangle-fill threshold) and can be modified if necessary. The activation sequence in the mapped chamber can also be represented as the propagation map, in which the whole chamber is blue and electrical activation waves are seen in red, spreading throughout the chamber as a continuous animated loop.

In addition, a voltage map, also color-coded, can be created and superimposed on the anatomic model to show the amplitudes of all selected points with red as the lowest amplitude and orange, yellow, green, blue and purple indicating progressively higher amplitudes. Myocardial scars are seen as low voltage, and their delineation may help in understanding the location of the arrhythmia, e.g. ventricular tachycardia (VT). Points can also be marked or tagged as “location only”, enabling one to return precisely to the region of interest after several points have been investigated or after an impedance rise is noted during the ablation procedure.

The electroanatomic model, which can be seen in a single view or in multiple views simultaneously and freely rotated in any direction, forms a reliable road map for navigation of the ablation catheter. Any portion of the chamber can be seen in relation to the catheter tip in real-time, and points of interest can easily be reached even without fluoroscopy. Most important, areas of previous ablations or points selected previously for ablation can be returned to easily. Potential ablation targets can be studied, compared and treated, if desired.

**Clinical applications:** The capability of the CARTO mapping system to associate relevant electrophysiologic information with the appropriate spatial location in the heart and to accurately determine the 3-D location and orientation of the ablation catheter is of great value in ablation procedures.¹⁹⁻³⁹

The technology enables the physician to both perform the mapping procedure and define the mechanisms underlying the arrhythmia. An ablation strategy can be more precisely designed and the system allows for a more accurate return to the locations of interest.

Over the last four years, over 2000 patients have been treated for various cardiac arrhythmias using the CARTO mapping system at our institution; Figs 6 to 18 are...
representative example of some of the arrhythmias mapped using this system in our institution. As shown in Figs 6 to 8, which depict atrial flutter, and Figs 12 to 15, which depict focal atrial tachycardia, differentiating between re-entrant and focal arrhythmia is made quite easy. Following identification of the mechanism involved in the genesis of the arrhythmia, the electroanatomic map generated can be used to design an appropriate ablation strategy. Defining the target sites for ablation is usually based upon a combination of anatomical and electrical criteria.

**CARTO strategy for specific arrhythmias:**

Atrial flutter: If the entire circuit is mapped, a re-entrant tachycardia such as atrial flutter is characterized by a range of activation times that will equal the cycle length of the tachycardia and also by close spatial orientation between arbitrary early and late sites (Figs 6 and 7). Following the usual anatomic landmarks mentioned before, our approach is to do a detailed tricuspid annulus/IVC isthmus mapping by withdrawing the catheter at 2–3 mm intervals and taking several points along the line. Voltage, activation and propagation maps are then created to look for any high-voltage areas which are better avoided in first-time ablations or to look for high-voltage and breakthrough sites during cases of recurrent atrial flutter, as these sites should be targeted under these circumstances. Bipolar electrograms recorded from the mapping catheter are filtered at 30–400 Hz. Areas showing <1 mV are considered to represent scar tissue. Our strategy is to ablate during atrial flutter; however, the ablation can be performed during sinus rhythm as well.

Ablation is usually performed at 50–60 °C for 30–60 s at each site. At the end of lesion delivery, if significant
Atrial activity is still visible, it is important to give more lesions or go around that site if it is identified as a high-voltage area.

Ablation success is defined by: (i) termination of atrial flutter during application of radiofrequency (RF) current (Fig. 8); (ii) inability to induce atrial flutter during programmed atrial stimulation at baseline and during isoproterenol infusion; and (iii) demonstration during pacing of a line of bi-directional conduction block between two points, i.e. from the coronary sinus ostium to the right atrium adjacent to the tricuspid annulus posterior and lateral to the ablation line (Figs 9 and 10). Immediately after ablation, a limited assessment is performed using 10–15 points during coronary sinus (CS) and low atrial pacing on either side of the ablation line. After waiting for 30–45 min, detailed mapping and programmed stimulation is repeated.

The main advantage of using the CARTO mapping system for atrial flutter is the visibility of an ablation line as it is performed so that no area is left out or repeatedly ablated. In patients with recurrent atrial flutter following previous ablation attempts, CARTO mapping is particularly helpful. As mentioned before, a detailed map of the isthmus is constructed. Since the system records both the activation time as well as the electrogram amplitude from each point selected, a voltage map which reveals the unablated area can be prepared. The RF energy can then be delivered to the site with more precision. The activation wave front during atrial flutter halts at the previously completed line but continues through the breakthrough site. As shown in Fig. 11, the CARTO mapping system is also useful for ablation of atrial flutter if recurrence occurs immediately following ablation.

Focal atrial tachycardia: In contrast to re-entrant arrhythmias such as atrial flutter, focal atrial tachycardia is characterized by a total range of activation times that are usually shorter than the cycle length of the tachycardia, and a very well-defined early activation site surrounded by later activation sites. An area of interest showing early activation is identified followed by detailed mapping of that area (Figs 12–15). As two simultaneous maps can be displayed on the CARTO mapping system, a precise site can be targeted. Furthermore, if unipolar electrograms at early right atrial septal sites show initial positive deflection, the location of tachycardia is most likely left atrial.
Simultaneous maps of the two atria can then be drawn (Fig. 14) to localize the earliest activation site.

Ventricular tachycardia: It has been shown that the chances of terminating VT are better if (i) RF current is delivered at sites where there may be entrainment with concealed fusion; (ii) the post-pacing interval approximates the tachycardia cycle length (<10 ms difference in cycle length); (iii) the stimulus to QRS duration is >60 ms or <70% of tachycardia cycle length; and (iv) there are mid-diastolic and pre-systolic potentials.33,34,39 Attempted RF ablation of VT, however, is quite complicated in patients with prior myocardial infarction (MI) because of broad re-entrant
circuits for VT. The prospect of success is even poorer when VT has multiple morphologies because of extensive myocardial scarring, or it causes rapid hemodynamic deterioration due to rapid heart rate and depressed left ventricular function. These features are often a contraindication to catheter ablation, as it is difficult to keep patients in tachycardia for a long time.

If it were feasible to interrupt broad re-entrant circuits by using lesions with RF ablation, catheter ablation could be successful but this requires capabilities beyond what can be achieved using conventional mapping techniques to identify the critical regions of slow conduction: (i) to precisely identify the margins of the scar; (ii) to identify and then return precisely to areas of interest; (iii) to visualize lines being created; and (iv) to perform ablation during sinus rhythm in unstable patients.

Such capabilities may now be feasible with the CARTO mapping system, which can be used to create 3-D maps of cardiac chambers, including those of the left ventricle.

In our laboratory, CARTO mapping is performed using a Navistar Cordis-Webster mapping and ablation catheter. The catheter is introduced and positioned in the left ventricle using a trans-septal or retrograde transaortic approach. During stable sinus rhythm, the margins of the left ventricle are defined by placing the catheter at the apex, sweeping it...
back to the base and margin under the mitral valve annulus and over other areas, such as the interventricular septum and the lateral walls. We prefer the trans-septal approach to prevent the repeated introduction of the mapping and ablation catheter through the aortic approach in case of a rise in impedance. The trans-septal approach also makes it easier to maneuver the catheter for mapping and ablation in the left ventricle.

After generation of the voltage map, pace mapping (at twice the diastolic threshold) is performed at the border of the scar tissue to replicate clinical and induced VT. Points that most closely matched these previously documented patterns of VT are tagged for ablation (Fig. 18). For a site to be considered appropriate, pace mapping has to mimic VT in at least 11 out of 12 leads. In cases of incessant, but tolerated VT, mapping can be performed during the VT. If VT occurs during pacing, the software allows switching between maps acquired during sinus rhythm and those acquired during VT. During VT, points are taken rapidly if the patient is hemodynamically stable, then accepted or rejected based on morphology, i.e. whether it was a QRS complex acquired during VT or an ectopic or fusion beat. Activation mapping is performed to assess the site of earliest breakthrough. Multiple points are taken and tagged, and these early points are then used for subsequent ablation.

For the purpose of delineating scar tissue, the infarcted myocardium is distinguished from healthy myocardium by a reduction in electrical voltage (bipolar voltage ≤1.0 mV).

After appropriate sites are identified by means of either pace mapping or activation mapping, the catheter is positioned at each site that had been tagged, and RF energy impulses (50–60 V for up to 60 s) are delivered to create lesions. If the electrograms at the catheter tip show approximately ≤50% reduction in amplitude, ablation is repeated in 30-s increments until the desired effect is obtained. Depending on the pace mapping technique, lesions are created at sites where 12-lead ECGs obtained during pacing most closely match the targeted VT. Next, a series of lesions are created, transecting the edges of the

Fig. 17. Voltage maps and sites of ablation in four different patients with ventricular tachycardias. A different view is shown in each patient.

Fig. 18. Detailed voltage map of a patient with extensive myocardial infarction shows extensive scar tissue. Red represents an area of dense scarring or of lowest voltage (amplitude ≤1.0 mV). Orange, yellow, green, blue and purple indicate progressively increased voltage and healthier tissue. The pink circle represents the site of the pace map which mimicked the ventricular tachycardia morphology most closely. Brown circles represent the lesion sites transecting the edges of the scar. The lesion sites are encircled with black to delineate the spots more clearly.
tachycardia. Furthermore, with any rise in impedance hemodynamic instability necessitate termination of switch rapidly between activation and pace mapping should stable VT, activation maps can be created and one may different morphologies. In the event of a hemodynamically why ablation at one region sometimes terminates VT of two slow conduction and the inner loop. This could also explain encompass all re-entrant zones, i.e. the outer loop, zones of create linear lesions across the edges of a scar which may voltage map can clearly identify areas of interest. Even though pace mapping may fail to precisely localize the zone of slow conduction. With pace mapping during sinus rhythm, it is difficult to map several areas and then go back to the most appropriate or optimal site. Hence, focal ablation of re-entrant circuits may be insufficient to interrupt these broad re-entrant circuits. The risk of hemodynamic collapse in patients who are unable to tolerate VT also frequently precludes successful mapping and ablation; such patients, including those in our study, have significant left ventricular dysfunction and large areas of scarring. Furthermore, should an impedance rise be noted during ablation using the fluoroscopic technique, it is difficult to return precisely to the original site.

To delineate myocardial scarring, the novel method of creating voltage maps of the left ventricle by means of CARTO mapping provides promising advantages, one being that maps can be created during sinus rhythm at leisure. Since, as mentioned earlier, the lower voltage of a myocardial scar accurately distinguishes it from healthy myocardium, in conjunction with the pacing technique the voltage map can clearly identify areas of interest. Even though pace mapping may fail to precisely identify a zone of slow conduction, ablation guided by CARTO mapping can create linear lesions across the edges of a scar which may encompass all re-entrant zones, i.e. the outer loop, zones of slow conduction and the inner loop. This could also explain why ablation at one region sometimes terminates VT of two different morphologies. In the event of a hemodynamically stable VT, activation maps can be created and one may switch rapidly between activation and pacemapping should hemodynamic instability necessitate termination of tachycardia. Furthermore, with any rise in impedance during the ablation, one can return to the exact site of previous ablation at any time because all ablation points have been tagged. Thus, by facilitating the creation of continuous lesions, CARTO mapping can benefit even patients who have refractory and hemodynamically unstable VT. This was clearly evidenced in our study by a statistically significant reduction in the number of shocks delivered by the implantable cardioverter–defibrillator (ICD) and antiarrhythmic medications in patients with very symptomatic and refractory VT.

Clinical implications: Electroanatomic mapping can thus greatly benefit patients with symptomatic, refractory tachycardia. Despite some limitations mentioned below, the capability of this technique to create several potential points of interest and return to them provides significant advantages over conventional techniques. Atrial flutter, especially recurrent flutter, can be ablated more precisely. The conjunctive use of voltage mapping and pace mapping during sinus rhythm can help in ablating even multiple hemodynamically unstable VTs. As for patients with hemodynamically tolerated VT, further studies are needed to assess whether this technique will obviate the need for an ICD or antiarrhythmic drug therapy.

Limitations of CARTO mapping: Creation of an electroanatomic map may be a lengthy process of tagging many points, depending on the spatial details needed to analyze a given arrhythmia. Since these points do not provide real-time, constantly updated information, more time may be needed for making new maps to see a current endocardial activation sequence, to detect a change in arrhythmia, or to fully visualize multiple VTs. To create optimum maps, sustained arrhythmia is usually needed to take enough data points.

Noncontact Mapping

The inability to accurately relate electrophysiologic information to a specific spatial location in the heart limits conventional techniques for RF catheter ablation of complex cardiac arrhythmias. Recent advances such as CARTO mapping offer advantages over conventional mapping by reconstructing a 3-D image of the cardiac chamber. However, in CARTO mapping, the degree of resolution is limited by the time available to acquire data points and, in many instances, use of the technique is restricted to hemodynamically stable and sustained arrhythmias. Arrhythmia mapping would be significantly advanced if clinicians had the ability to collect thousands of data points in a single beat without the need for point-by-point contact.
electrograms. A high-resolution noncontact mapping system capable of single-beat mapping has been validated in humans\textsuperscript{40–52} and has been used at our institution over the past 2 years in over 200 patients with complex cardiac arrhythmias. These included patients with atrial flutter, VT, atrial tachycardia and atrial fibrillation (AF).

**Fundamentals of the noncontact mapping system:**

The mapping technique using the EnSite 3000™ (Endocardial Solutions, St Paul, MN) mapping system has been studied extensively. This technique is based on the premise that endocardial activation creates a chamber voltage field which obeys Laplace's equation (Fig. 19). Noncontact intracavitary electrodes can be used to detect the potential field on the endocardial surface. The potentials in this field are generally lower in amplitude and frequency than the source potential of the endocardium itself, which limits their utility in the raw form. To improve accuracy and stability in reconstructions, an inverse Laplace's equation is used. Once the potential field has been established, over 3000 activation points can be displayed as computed electrograms or as isopotential maps. A three-step process of establishing geometry, identifying the area of interest and navigating the ablation catheter in this area is used to map and treat arrhythmias.

The balloon or multielectrode array (MEA) comprises a braid of 64 polyamide-insulated, 0.003" diameter wires (Fig. 20). For electrophysiologic studies, any mapping catheter can be used. The catheter location system uses a low-level, 5.68 kHz current emitted by the distal electrode which returns to each of the two intra-chamber ring electrodes on the MEA (Fig. 21). Since the positions of both the array electrodes and the current-sink electrodes are known, a custom algorithm is generated to determine the position of the roving catheter by demodulating the 5.68 kHz potentials on the MEA. The locator system serves several purposes:

1. **Three-dimensional modeling:** As a conventional catheter moves around the cardiac chamber under fluoroscopic and electrophysiologic guidance, a series of coordinates are built within the endocardium from which a contoured model is constructed.
generated (Fig. 22). To accomplish this, the system automatically stores only the most distant points visited by the catheter, then uses a bicubic spline-smoothing algorithm to create a high-resolution contoured model of the chamber. By gating each sample to a surface-lead R wave, a contoured wire frame model with end-diastolic dimensions is created (Fig. 22).

(2) Catheter guidance and location: The locator signal can also be used to display and log a catheter's position within the endocardial model and to guide it to the region of interest for ablation.

The MEA is deployed in the cardiac chamber of interest and the geometry created. Once the chamber geometry has been delineated, tachycardia is induced and the tachycardia site mapped using the EnSite 3000™ system. As the electrical activity within the endocardium is sensed by the MEA's microelectrodes, the array potentials are sampled at 1200 Hz and passed to a higher-order boundary element computation. The boundary element uses an inverse formation to solve LaPlace's equation for each sample, yielding endocardial potentials. Using this method, more than 3000 isopotential points are generated and may be displayed as computed (virtual) electrograms and as isopotential maps.

The EnSite 3000™ system reliably replicates the voltage electrogram signal displayed by the contact catheter electrodes. In a study that compared contact recordings with computed electrograms during sinus rhythm and pacing, a mean correlation of 0.96 was demonstrated in reproducing morphology. When pacing techniques were used in this study, the distance from the RF lesion to the pacing plunge electrode was approximately 4.0±3.3 mm (mean 3 mm).44

**Principle of inverse solutions and filter settings:** The electrical activity detected by the electrodes on the surface of the MEA is generated by the potential field on the endocardial surface of the chamber of interest. As discussed, the potential distribution on the MEA created by the endocardial activation is described by LaPlace's equation, $s^2V=0$. The highest chamber voltage is at the site of origin of the electrical impulse. Although the electrode closest to the origin of the impulse is influenced the most, all the electrodes on the MEA are influenced, the degree of influence diminishing with the distance between the electrode and each endocardial point.

The electrograms detected by the noncontact MEA are of lower amplitude and frequency than those detected at the source by contact electrograms which, in turn, limits the utility of contact electrograms in raw form.49–56 A technique called the boundary element method (BEM), based upon the inverse solution to LaPlace's equation is used. The potential field created on the MEA surface depends upon the geometry of both the MEA and the endocardium and their relationship in space. The MEA geometry is determined at the time the catheter is manufactured while the endocardial geometry is obtained at the time of geometric reconstruction as described above. With this information, it is then possible to compute endocardial electrograms from the MEA potentials by inverse solution of LaPlace's equation.

There are regions of complex electrical phenomena that are computed into smaller regions so that behavior within the element can be accurately determined using the Finite Element Method (FEM). The properties of electrical conduction between such different elements are equated, resulting in a linear system of many equations. The BEM works similar to the FEM but only the two-dimensional (2-D) surface (i.e. the boundary) is modeled rather than the entire 3-D domain, resulting in far fewer elements and equations to deal with.

However, small noise in the measured potentials in the cavity could potentially lead to large errors in the reconstructed endocardial electrograms if careful attention is not paid to the application of this method. The technique of regularization is used to overcome this problem.55,56 Several sources of noise can affect the recording and include:

(1) electrical interference from the surrounding environment;
(2) electrochemical fluctuations at the surface of the recording electrodes; and
(3) noise from the amplifier circuitry due to electrical fluctuations.

Environmental noise comes primarily from power lines and manifests as common-mode noise across the body. Electrical artifacts fall into three categories:

(1) Main power supply noise, i.e. 50–60 Hz. This noise is a characteristic of the local electrical power source. It is a medium-frequency noise which is usually steady in amplitude.

(2) High-frequency noise is a random noise which is usually the result of using many electrical devices on the same power source. This noise does not always have a steady amplitude and usually manifests as a thickening of the signal recording.

(3) Low-frequency noise is a random noise which makes the ECG signals appear as if they “float” on waves.

Common-mode noise is rejected by connecting a unipolar reference to the bipotential amplifiers in the standard differential configuration. Noise due to electrochemical fluctuations at the surface of the electrodes is primarily low frequency in nature and is reduced by coupling the electrodes to the amplifiers through a high-pass filter which attenuates frequencies below 0.1 Hz.

The small noise fluctuations in amplifier circuitry are generally broadband in frequency and are uncorrelated between channels. Regularization is required to attenuate these random fluctuations and any residual noise that remains after reduction of the main power supply, high- and low-frequency noise (described earlier). Random fluctuations between amplifier channels translate into errors in measurement at the recording sites which are randomly associated with these sites. These errors can be thought of as small and rapid fluctuation steps of potential across the surface of the MEA. Regularization attenuates these rapid fluctuations across space at any given instant in time much as a low-pass filter would attenuate rapid fluctuations across time at any given point in space.

The accuracy of the noncontact mapping system thus depends on inverse solutions and a methodology which, in turn, will depend upon accurate and detailed geometric creation. In addition, the accuracy will depend upon the applied regularization technique. Several techniques have been used to improve the accuracy of the process of regularization. The geometry and voltage are modeled using bicubic spline surfaces instead of the standard linear elements. This allows for a more physiologically realistic model of the endocardium. Small errors in the model may still occur, however, due to undersampling of the endocardial points or due to complexity of the chamber geometry.

**Reconstruction of the map and mapping protocol:** The MEA is deployed in the cardiac chamber of interest and the mapping catheter is then moved to known anatomical locations which are tagged. A detailed geometry of the chamber is then reconstructed by moving the mapping catheter around the chamber. Unlike the CARTO mapping system, the noncontact system allows for the patient to be in sinus rhythm or tachycardia during creation of the geometry. A activated clotting time (ACT) is kept at 250 s and 300 s for right-sided and left-sided mapping, respectively.

The noncontact mapping system is capable of reconstructing and interpolating more than 3000 unipolar electrograms over the endocardium during mapping and, in turn, isopotential or isochronal maps can be reconstructed from these electrograms. The color range represents voltage or timing of onset. In addition, electrograms (virtual electrograms) may be selected using the mouse from any part of the created geometry and displayed as waveforms.

Because BEM is used for inverse solutions, the 3-D myocardium is treated as a 2-D endocardial surface. The reconstructed electrograms are subject to the same electrical principles as contact catheter electrograms, as they contain far-field electrical information from the surrounding endocardium as well as the underlying myocardium signal vector, and distance from measurement can affect the contribution to the electrogram. Although structures such as the papillary muscles may contribute to the reconstructed electrograms, their contribution is not significant relative to the much larger area of the surrounding endocardium.

**Validation of reconstructed electrograms:** Noncontact mapping has been validated in several studies. In the study by Gornick et al. four methods of validation were used: (i) driven electrodes in an in vitro tank were located; (ii) waveforms generated from an array catheter were compared with catheter contact waveforms in canine left ventricles; and (iii) sites of local left ventricular endocardial activation were located and marked with RF lesions. Tank testing located a driven electrode to within 2.33±0.44 mm. Correlation of timing and morphology of computed versus contact electrograms was 0.96. Radiofrequency lesions marked 17 endocardial pacing sites to within 4.0±3.2 mm. However, the accuracy of the location changes the further the distance from the center of the balloon.

Although electrograms recorded by contact and
reconstructed noncontact electrograms are similar in both near- and far-field components of electric potential, there may be variations. In several studies, results from 34 left ventricular electrograms were compared to contact electrograms, demonstrating a mean timing difference of 0.9 ms and a mean morphology cross-correlation of 0.83 over a population of 31,000 recorded cycles. One-half of the time differences were within 2 ms and 77% were within 10 ms.

**Clinical applications:** Over the past 2 years, noncontact mapping has been used in our laboratory to treat over 200 complex cardiac arrhythmias. Some representative examples are depicted in Figs 23 to 30.

**Atrial flutter:** The patient mapped in Fig. 23 had atrial flutter which was ablated at the time of mitral valve surgery using a malleable EP Technologies™ RF probe (Boston Scientific, San Jose, CA). However, 3 weeks after surgery, the patient was admitted with dyspnea and palpitations. The surface ECG of the tachycardia was again suggestive of atrial flutter with typical negative “saw tooth” waves on the inferior ECG leads.

Using the EnSite 3000™ noncontact mapping system, the activation sequence of the re-entrant circuit in the right atrium was revealed to be counterclockwise atrial flutter. Detailed mapping identified the breakthrough site in the isthmus (Fig. 23a). A computed electrogram showed double potentials at the sites of block and continuous conduction through the site of “gap”. Following overdrive pacing of the atrial flutter, bi-directional conduction over the gap was confirmed during pacing from the low lateral right atrium and the CSO (Fig. 23b). Three lesions were delivered at the “gap” site. Radiofrequency ablation performed at the “gap” following induction of atrial flutter terminated the tachycardia.

To confirm the absence of conduction across the isthmus following ablation, atrial pacing was done from the proximal
that the leading edge of a wavefront of atrial depolarization spread out from that site. Following RF ablation at this site, the tachycardia was noninducible despite an aggressive stimulation protocol, including programmed stimulation and burst atrial pacing at baseline and during isoproterenol infusion. The time to prepare the balloon catheter and reconstruct right atrial geometry was 5 min and 19 min, respectively. During follow-up of 11 weeks, the patient has had no recurrence of arrhythmia and is off all medications.

Atypical atrial flutter and atrial fibrillation (AF) originating from the right atrium: In the patient depicted in Fig. 25, several documented prior tracings were suggestive of paroxysmal atrial fibrillation (AF), typical atrial flutter with "saw tooth" flutter waves in the inferior leads and, possibly, atrial tachycardia. Based upon cardiac evaluation prior to the referral, including cardiac catheterization, there was no evidence of coronary artery disease. Because flecainide and amiodarone did not control his symptoms adequately, the patient underwent electrophysiological evaluation and RF catheter ablation. Right atrial geometry was created using the EnSite 3000™ noncontact mapping system. During atrial pacing, typical atrial flutter with counterclockwise rotation was easily induced, mimicking one of the documented arrhythmias.
Catheter ablation of the tricuspid–IVC isthmus led to termination of the atrial flutter. Postablation, bi-directional block across the isthmus was demonstrated, as in the patient described earlier, during pacing from the coronary sinus and low lateral right atrium.

Following ablation of typical atrial flutter, the patient had a spontaneous episode of AF similar to one of his documented arrhythmias. Evaluation of the reconstructed electrograms showed a premature atrial beat degenerating into AF. Sequential isopotential maps (Fig. 25a) showed the ectopic activation waveform spreading out from the region of the mid crista terminalis. Following ablation at this site and during programmed atrial stimulation, a third tachycardia was induced. A positive P wave morphology was seen on the inferior ECG. This third tachycardia was thought to be similar to one of his clinical tachycardias as well; however, noncontact mapping using isopotential maps showed an atypical nonisthmus-dependent atrial flutter (Fig. 25b). Radiofrequency lesions transecting the narrowest conduction zone successfully terminated the tachycardia. Time to prepare the balloon catheter and to reconstruct the right atrial chamber were 4.5 min and 16 min, respectively. During a follow-up of 4 months, the patient has stayed free of arrhythmias and is off all medications.

Atrial fibrillation originating from the pulmonary veins: Figure 26 depicts a 63-year-old man with a history of symptomatic persistent AF and hypertension but no coronary artery disease. He had an estimated left ventricular ejection fraction of 40% and an enlarged left atrium (4.8 cm). While on sotalol, the patient had premature atrial contractions (PACs) which reinitiated AF following two external cardioversion attempts. Following this, the patient was placed on amiodarone for 4 weeks, then...
externally cardioverted again. Two days later, the patient was readmitted with dyspnea and palpitations and found to be back in AF with a rapid ventricular response. Amiodarone was discontinued and the ventricular rate controlled with beta-blockers and calcium-channel blockers. Three weeks later, he was brought in to the laboratory for mapping and ablation of AF.

The MEA and mapping catheter were placed in the left atrium using a trans-septal approach and 3-D reconstruction was performed. Transesophageal echocardiography, which had also been used to perform the trans-septal catheterization, confirmed the location of the pulmonary veins, and these sites were tagged. Following external cardioversion, the patient had frequent PACs, but no AF was reinitiated. Mapping of the left atrium showed the origin of the PACs to be the right superior pulmonary vein.

Following ablation at this site, during a 20-week follow-up period, the patient remained free of AF on half the dosage of amiodarone (200 mg/day) which had failed to maintain sinus rhythm prior to ablation. At the last follow-up visit, the patient had remained free of AF for 12 weeks and was off amiodarone entirely. Time to prepare the balloon and reconstruct the left atrium were 4 min and 29 min, respectively, and the total procedure time was 167 min.

**Myocardial ventricular tachycardia:** Figure 27 depicts a 69-year-old man with a history of ischemic cardiomyopathy, a left ventricular ejection fraction of 19% and VT for which he had received an ICD. The patient had received over 50 shocks from the ICD during a period of 3 months despite a trial of antiarrhythmic medications including sotalol, procainamide, mexiletine and amiodarone. During programmed ventricular stimulation, sustained monomorphic VT similar to his clinical VT was induced with QRS morphology of right bundle branch block (RBBB) and left-axis deviation in young patients who have no structural disease has been reported. Endocardial activation mapping during VT can identify the earliest site of activation in the inferoposterior left ventricular septum. High-frequency potentials 30–40 ms before the VT–QRS complex, thought to represent Purkinje potentials, have been identified in some patients and these data have been used for VT ablation. In this example, single-beat mapping using data derived from a noncontact mapping technique was used to delineate a part of the tachycardia circuit in a young patient with recurrent VT (Fig. 28) and identify mid-diastolic potentials, thus helping to define the mechanism of the tachycardia (Figs 29 and 30). The information was then used to identify the appropriate site for successful ablation. The MEA was deployed in the left ventricle via a retrograde transaortic approach and a 7 F mapping and ablation EP Technologies™ catheter (Boston Scientific, San Jose, CA) was deployed via a trans-septal puncture. Once left ventricular geometry was delineated, VT was induced and the site of tachycardia mapped using the EnSite 3000™ system. Mid-diastolic potentials were identified on computed electrograms (Fig. 29) and confirmed to be part of the tachycardia circuit when a premature ventricular contraction was found to be resetting the VT without altering the duration of QRS. Activation from the potential inscribing the QRS on the surface electrogram was noted to spread over the Purkinje fascicle network before exiting.

**Idiopathic left ventricular tachycardia:** Ventricular tachycardia with QRS morphology of right bundle branch block (RBBB) and left-axis deviation in young patients who have no structural disease has been reported. Endocardial activation mapping during VT can identify the earliest site of activation in the inferoposterior left ventricular septum. High-frequency potentials 30–40 ms before the VT–QRS complex, thought to represent Purkinje potentials, have been identified in some patients and these data have been used for VT ablation. In this example, single-beat mapping using data derived from a noncontact mapping technique was used to delineate a part of the tachycardia circuit in a young patient with recurrent VT (Fig. 28) and identify mid-diastolic potentials, thus helping to define the mechanism of the tachycardia (Figs 29 and 30). The information was then used to identify the appropriate site for successful ablation. The MEA was deployed in the left ventricle via a retrograde transaortic approach and a 7 F mapping and ablation EP Technologies™ catheter (Boston Scientific, San Jose, CA) was deployed via a trans-septal puncture. Once left ventricular geometry was delineated, VT was induced and the site of tachycardia mapped using the EnSite 3000™ system. Mid-diastolic potentials were identified on computed electrograms (Fig. 29) and confirmed to be part of the tachycardia circuit when a premature ventricular contraction was found to be resetting the VT without altering the duration of QRS. Activation from the potential inscribing the QRS on the surface electrogram was noted to spread over the Purkinje fascicle network before exiting.

**Fig. 27.** Ventricular tachycardia circuit mapping. Sequential isopotential maps of the left ventricle surface ECG leads and reconstructed electrogram (1–5) during ventricular tachycardia are shown. At the end of ventricular depolarization, as shown by the timing of the cursor on the reconstructed electrograms, a zone with no depolarization is seen on the isopotential map. Timing of the endocardial activation is represented by the yellow cursor; end of depolarization (Frame A); spread of activation over the diastolic pathway (Frames B to C); and exit site of the circuit (Frames E to F); which is confirmed by the presence of the cursor at the inscription of the QRS complex on surface ECG. Thus, a zone of slow conduction during diastole was identified and targeted for ablation. From: Sra et al. Noncontact mapping for radiofrequency ablation of complex cardiac arrhythmias. J Interven Card Electrophysiol 2001; 5: 329. Reproduced by permission.
thus identifying part of the circuit. Ablation at the site of the mid-diastolic potential successfully ablated VT with no further initiation of the tachycardia. During a 4-month follow-up, this patient has been free of symptoms and has not needed medication.

Clinical implications: Noncontact mapping, whose hallmark is single-beat mapping, is thus an important development in the management of cardiac arrhythmias. Noncontact mapping may be particularly helpful in patients who have recurrent atrial flutter following a previous ablation because it can identify the "gap" or breakthrough site, which can then be targeted precisely. As any number of maps can be superimposed on the initial geometry, bidirectional block at the ablation site can be rapidly identified during pacing following ablation. Tagging ablation areas during delivery of each RF impulse and a constantly visible ablation line offer another advantage; they ensure that no area is overlooked or ablated repeatedly.

Atypical atrial flutters are characterized by macro re-entrant tachycardias that do not use the tricuspid–IVC–Eustachian ridge isthmus and do not exhibit re-entry around atrial incisions. Because this arrhythmia is complex and conventional mapping is inadequate, data about various forms of atypical flutter in humans are currently inadequate and, in most cases, treatment has been restricted to pharmacological management. As shown in this report, noncontact mapping may be particularly helpful in delineating macro re-entrant circuits and, more importantly, identifying the precise location where ablation may terminate this type of tachycardia.

In patients who have nonsustained ectopic atrial tachycardia, noncontact mapping may allow rapid localization of the arrhythmic focus by simply selecting an area of interest that shows the earliest endocardial activation on the initial map and creating a detailed map of this area using a single-beat mapping technique. Our approach is to start with a right atrial map, but the left atrium is mapped if the point of earliest activation is in the septal region and has an initial positive deflection on reconstructed electrograms or if the surface ECG is suggestive of left atrial tachycardia.

Identifying trigger sites of pulmonary vein ectopy is another potential advantage of the noncontact mapping system. As recent studies have shown, pulmonary vein
ectopy initiates AF in many patients. The presence of ectopy occurring spontaneously during various electrophysiological maneuvers as well as that initiating AF following external cardioversion can all be used to identify ablation sites. None of these are readily identified by sequential mapping using conventional techniques. The task is further complicated by unpredictable and inconsistently inducible PACs. However, high-resolution 3-D reconstruction of the left atrium (over 3000 reconstructed electrograms) coupled with single-beat mapping makes it possible to precisely map these targets in patients with infrequent PACs from just a single beat.

Despite ICD implantation, recurrent VT can cause mortality and significant morbidity. For catheter ablation to succeed, it is critical to identify its re-entrant circuits, including zones of slow conduction and reentry site, which is suggested by inscription of the QRS complex on the surface electrocardiogram as the wavefront exits from such regions. Using conventional techniques, it has been shown that the chances of terminating VT are better if RF current is delivered at sites where: (i) there may be entrainment with concealed fusion; (ii) the post-pacing interval approximates the tachycardia cycle length; (iii) the stimulus to QRS duration is >60 ms; and (iv) there are mid-diastolic and pre-systolic potentials. However, with conventional mapping in patients who have rapid hemodynamic deterioration due to rapid rate and depressed ventricular function, the prospects of success are poor because it is not possible to keep these patients in tachycardia during mapping. A preferable alternative in such unstable patients—now feasible with noncontact mapping—is to create linear lesions that transect critical regions, i.e. areas of slow conduction, and then return precisely to areas of interest, visualizing lines of ablation as they are being created and performing the ablation during sinus rhythm (Fig. 31). As stated earlier, comparing reconstructed and contact electrograms recorded from the same site during VT has shown an excellent cross-correlation of 0.86±0.16 and a mean time error of 1.67±10.06 ms, validating its accuracy.

Zipes et al. identified the following triad of diagnostic characteristics for this VT: (i) induction by atrial pacing; (ii) a configuration of RBBB with left-axis deviation; and (iii) no structural heart disease. Subsequently, Belhassen et al. demonstrated the sensitivity of this VT to verapamil. Debate has also centered on whether this tachycardia is re-entrant or triggered. It has also been proposed that the tachycardia circuit may be focal as suggestions have been made that ventricular extrasystoles can capture the ventricle without resetting the VT. Termination of the tachycardia with programmed stimulation, an inverse relationship between the extrastimulus and the first VT beat, entrainment criteria, and mid-diastolic potentials are suggestive of re-entry with an excitable gap as a mechanism of VT. Okumura et al. were able to make several observations regarding the entrainment of the tachycardia: (i) there was pacing with constant fusion with the last captured electrogram being entrained but not fused; and (ii) with increased pacing rate, there was progressive but constant fusion and the activation site was not captured anterograde (direct capture rather than orthodromic capture). It has also been suggested that, due to closeness of the site to the posterior fascicles, entrainment is more frequently achieved when pacing is accomplished from the right ventricular outflow tract rather than from the right ventricular apex. Successful ablation at sites demonstrating potentials originating in the Purkinje fibers suggest that these may be part of the tachycardia circuit. In a study by Nakagawa et al., distinct Purkinje or p potentials were indentified preceding the QRS during tachycardia by 15 to 42 ms. In some instances, mid-diastolic potentials have also been described. Due to ablation at different sites in the left ventricle, it has also been suggested that this arrhythmia entity may not represent a homogenous group. Although pace mapping has been used during VT ablation, the data derived are often insufficient.

In the example described in this manuscript, noncontact mapping technology, by acquiring extensive data to create an activation sequence simultaneously during a single beat of tachycardia, was able to delineate some of the physiological aspects of this intriguing arrhythmia. Unlike observations in prior studies, the precise delineation of part of the tachycardia circuit does not suggest that this is focal. Furthermore, the re-entrant mechanism of the tachycardia is validated. These findings are further corroborated by the discovery that a single premature ventricular beat was able...
to reset the tachycardia without altering the relationship between the potential and the onset of the QRS. A 79 ms potential-to-QRS distance suggests that this was not a Purkinje potential as described in some earlier studies. Nor was this seen during sinus rhythm. There are insufficient data to indicate any significant conduction system disease in these patients.

The zone of slow conduction has been thought to be dependent upon slow inward calcium current.74,75 Also, the role of verapamil in some of these tachycardias confirms this hypothesis. The tachycardia circuit involved the Purkinje fascicle network, which may have been significantly diseased as suggested by prolonged conduction time from mid-diastolic potential to onset of QRS on the surface electrogram. These findings suggest that some disease in the Purkinje system, by enabling a slowing of conduction, may create the conditions for a re-entrant tachycardia to occur.

Limitations: Although noncontact mapping is new and exciting, there are limitations to this technique. Caution will be needed to interpret the great amount of new data not previously available by any prior technology. The overall accuracy of the reconstructed electrograms may decrease with distance of the area mapped from the MEA, thus creating problems in mapping large cardiac chambers. Although the risk of complications is low, aggressive anticoagulation measures because of MEA deployment in the cardiac chamber expose patients to potential bleeding complications. The ACT needs to be kept around 250 s for the cardiac chamber expose patients to potential bleeding complications. The ACT needs to be kept around 250 s for anticoagulation measures because of MEA deployment in the cardiac chamber expose patients to potential bleeding complications.

Acknowledgment

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Carotid Artery Stenting: Current Status and Future Prospects

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Carotid artery stenting (CAS) has emerged as an endovascular treatment alternative to carotid endarterectomy (CEA) for the management of atherosclerotic obstructive extracranial carotid artery disease. Evidence is accumulating in support of its efficacy in preventing stroke. This treatment modality is being increasingly utilized to treat the high-risk surgical population and randomized trials have been undertaken to compare its efficacy with that of CEA. More suitable equipment and distal protection devices currently under evaluation are expected to enhance the procedural safety and clinical outcomes of this treatment. This article discusses the current indications, patient selection and future prospects of CAS.

Surgical Background

The clinical significance of an endovascular approach to occlusive disease of the carotid artery is best understood in the context of its surgical counterpart, CEA. Based on three landmark randomized trials comparing CEA with medical therapy, the former is considered to be the standard treatment for both symptomatic and asymptomatic extracranial carotid artery stenoses. However, the appropriate clinical indication for CEA requires careful analysis of the population studied in these trials and the results obtained. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) yielded the largest and most rigorously collected data with a neurological overview and provides a unique insight into the outcome of CEA when performed in centers of excellence. In this study, CEA combined with the best medical therapy was clearly superior to medical therapy alone in reducing the risk of stroke in a select group of patients with symptomatic extracranial carotid artery stenoses of ≥50%. This benefit was directly related to the severity of stenosis and was greatest for patients with stenoses of ≥90%. The overall combined 30-day rate of stroke and death in the CEA group was 6.7%.

The second important study that examined the benefit of CEA in symptomatic patients was the European Carotid Surgery Trial (ECST) which also demonstrated a clear benefit of surgery over medical therapy in reducing the risk of future stroke. The overall 30-day incidence of stroke and death in the surgical arm was similar to that seen in NASCET but was higher in women (10.6%), in patients with a systolic blood pressure >180 mmHg (12.3%) and in the presence of peripheral vascular disease (12.3%). The Asymptomatic Carotid Atherosclerosis Study (ACAS) also showed a clear benefit of CEA plus medical therapy in patients with asymptomatic extracranial carotid artery stenosis of ≥60%. In this study, the estimated 30-day perioperative risk of stroke or death was 2.7%. The population in this study was at low risk for CEA, as patients with important common co-morbid conditions were excluded. In all these trials, CEA was complicated by cranial nerve palsies in approximately 7% of the patients, and in 13% there were a variety of local wound problems or medical complications including congestive heart failure, myocardial infarction and cardiac arrhythmias. These operative complications are important since they are negligible in patients undergoing CAS.

Despite the benefit observed in these trials, their results cannot be extrapolated to the general population, largely because the risk of CEA is likely to be significantly higher in the excluded population. These include patients with common conditions such as prior ipsilateral CEA, significant coexisting coronary artery disease, as well as those with significant renal, hepatic or pulmonary co-morbidities. Numerous observational studies have reported increased rates of perioperative stroke and death in these groups. In addition, patients who underwent CEA in the presence of an occluded contralateral carotid artery had high perioperative combined stroke and death rates (14%). Therefore, the perceived benefit of CEA in these patients may not be the same as that seen in the randomized population.

Further, these trials were conducted by pre-selected high-volume surgeons who qualified for participation only if they demonstrated low perioperative stroke or death rates. Recent data, however, have shown definitive evidence that the actual incidence of stroke and death from CEA in...
the community is much higher than that reported in randomized trials.\textsuperscript{15–17} Data from Medicare mortality statistics also showed that in-hospital mortality (not the more rigorous 30-day neurological assessment) was significantly higher in low-volume CEA centers than in high-volume ones, and was higher in the latter than in NASCET/ACAS centers (2.5%, 1.9% and 1.4%, respectively).\textsuperscript{18} Approximately 80% of CEAs in the United States are performed in low-volume hospitals by operators carrying out less than 20 procedures annually.\textsuperscript{19} Moreover, published CEA outcomes are greatly influenced by the manner in which they are reported; specifically, stroke rates reported by surgeons were lower (2.2%) than those reported when neurologists were also involved in the authorship (7.7%).\textsuperscript{19–20}

Accepting these limitations, the American Heart Association has set guidelines for the performance of CEA. According to these, CEA should be performed only if the combined stroke and death rates can be kept at ≤6% in symptomatic and <3% in asymptomatic patients with severe extracranial carotid artery stenoses.\textsuperscript{21}

**Rationale for an Endovascular Approach**

The documentation of a significant incidence of both neurological and non-neurological complications associated with CEA in landmark studies emphasizes the need to pursue an alternative and safer method for treating carotid bifurcation disease, especially in a subset of patients thought to be at high risk from CEA.

Carotid artery stenting is an endovascular, less invasive treatment approach which offers several advantages. The majority of CEAs are still carried out under general anesthesia with recognized attendant risks, especially from frequently coexisting coronary artery disease or heart failure. In addition, neurological complications are only apparent following recovery from anesthesia. In contrast, stenting is performed in the nonsedated conscious patient; under these conditions, neurological changes are immediately recognized and diagnostic intracranial angiography and appropriate therapeutic measures can be promptly initiated.

Carotid endarterectomy is difficult in patients with high carotid artery stenoses or bifurcations, those with proximal/ostial common carotid artery (CCA) lesions and short, obese necks. In these situations, extensive exposure of the carotid artery is required, which adds considerable risk to the procedure. Patients with prior irradiation to the neck for head and neck cancers and prior radical neck dissection also present a challenge for the surgeon due to the unusual location of the lesions and extensive fibrosis in and around the arterial wall. Similarly, patients with restenosis after prior CEA are sometimes at higher risk for repeat CEA due to scarring. These conditions usually require general anesthesia and some may require mobilization of the mandible. It is also more difficult for the surgeon to expose the artery for shunt placement. Fibrosis and scarring around the artery require extensive dissection, increasing the risk for cranial nerve injuries and lead to delayed wound healing. In some patients, CEA cannot be performed and an interposition graft might be required. Generally, none of the above conditions are a problem for the endovascular approach and, accordingly, CAS may clearly be preferable in these patients.\textsuperscript{22–24} In addition, stenting offers the potential advantages of a shorter hospital stay, shorter recovery period and reduced cost.

**Patient Selection**

The current indications for CAS are predominantly determined by the operator's experience and results. In general, there should be no contraindication to proceed with stenting, provided the procedure can be performed with a combined stroke and death rate of ≤6% in symptomatic and <3% in asymptomatic patients.\textsuperscript{25} Similarly, based on the current knowledge of surgical outcome of carotid artery disease, stenting should only be carried out in lesions in which stenosis is ≥50% in symptomatic and ≥70% in asymptomatic patients (using NASCET angiographic measurements).\textsuperscript{25} The risk/benefit ratio of the procedure for an individual patient should be established prior to the intervention. Based on our learning curve experience and current technology, several factors associated with increased or decreased risk of procedural events have been identified (Table 1). However, as technology improves, particularly with the application of cerebral protection devices, these factors may need to be revised.

During the initial learning curve of the operator, cases associated with higher periprocedural risk should be avoided and those with low procedural risk selected. In these patients, especially those below the age of 80 years, stenting is associated with a low rate of periprocedural events (Table 2). In higher-risk subsets, much greater experience is required to achieve similar results. Our current practice is to treat high-risk patients, especially the elderly, with distal protection. Although at the beginning of the learning experience there is a tendency to accept high-risk patients for CEA, this temptation should be avoided if the patient has one or more of the higher-risk descriptors listed in Table 1. A number of situations that pose a high risk for
CEA may, however, be at low risk for stenting and represent ideal indications, such as restenosis after prior CEA or stenoses in those with prior neck irradiation and/or radical neck dissection. Patients with discrete proximal or ostial CCA lesions, discrete lesions in the distal internal carotid artery (ICA) or lesions involving high bifurcations are also considered ideal candidates for stenting.

It must be emphasized that unfavorable lesion characteristics may only be apparent following initial angiography. The operator should be prepared to abandon the procedure at this point and consider elective CEA or decide whether to continue medical management. The judgement of the operator is critical in achieving a low complication rate. Since there are usually reasonable alternative therapies, it must be emphasized that failure to complete the procedure is acceptable but an avoidable complication is not.

**Clinical Results**

Over the past 5 years, we challenged this new technique by treating a skewed, high surgical-risk population which had been excluded from prior randomized CEA trials. A large number of these patients were referred by physicians, including vascular surgeons, because of a variety of conditions that put them at higher risk for CEA. These conditions included: prior ipsilateral CEA, prior ipsilateral neck irradiation, contralateral occlusion and severe coexisting coronary artery disease requiring staged/simultaneous carotid and coronary artery intervention. In addition, a variety of distally located lesions, high bifurcations and proximal CCA disease were treated. All varieties of lesions were attempted, including severely ulcerated or calcified lesions, long severe lesions, “string sign lesions” and completely occluded vessels. Similarly, all types of severely diseased aortic arch vessels, including tortuous, calcified, atherosclerotic and stenotic CCAs were accessed to complete the procedure. In general, our patients belonged to an older age group (mean age: 69±10 years) who suffered from a number of co-morbidities including coronary artery disease, hypertension and diabetes mellitus.

From September 1994 through May 2001 we completed stenting of 935 hemispheres in 847 consecutive patients. The overall 30-day all-stroke and death rate was 7%. The 30-day mortality was 1.3%, and major and minor disabling stroke rates were 0.9% and 4.7%, respectively. The technique has gained wide acceptance at present because major adverse events have been uncommon and minor strokes (usually noted only during detailed examination by the neurologist) have not been of functional significance to the patient. Neurological events continue to be mostly non-disabling strokes. Deaths and disabling strokes have been uncommon, especially in patients <80 years. While the rate of embolic events in patients below the age of 80 years has been very low, higher rates of neurological complications were seen in patients ≥80 years. Over our 5-year experience, we have modified the eligibility criteria.

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<th>Patients at increased risk for neurological complications</th>
<th>&lt;80 years</th>
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<tr>
<td>Clinical</td>
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<tr>
<td>Advanced age (≥80 years)</td>
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<td>Prior major disabling stroke, or cerebral atrophy/dementia</td>
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<td>Unstable neurological symptoms (recent TIA or stroke)</td>
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<td>Anatomical</td>
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<td>Severely tortuous, calcified and atherosclerotic aortic arch/arc vessels</td>
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<td>Severe tortuosity just distal to the bifurcation</td>
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<td>Coexisting proximal common carotid artery lesion</td>
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<td>Total occlusion or long sub-total occlusions— “string sign lesions”</td>
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<td>Severe concentric calcification</td>
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<td>Angiographic evidence of a large thrombus</td>
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<th>Patients at lower risk for embolic events</th>
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<td>Age ≤80 years</td>
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<td>Less severe stenosis</td>
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<td>Anatomical</td>
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<td>Straight, noncalcified, “smooth arch vessels”</td>
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<td>Nontortuous bifurcation</td>
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<td>Absence of common carotid artery disease (except at adjacent bifurcation)</td>
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<tr>
<td>Absence of thrombus</td>
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<td>Absence of kinks, loops, bend-points at lesion site</td>
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<td>Short lesions</td>
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<td>Prior CEA</td>
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Values in parentheses are percentages
We now strongly believe that given the availability of current technology and taking into account the experience of the operator, careful patient selection is critical for maintaining low complication rates. Our recent experience at the Lenox Hill Hospital is summarized in Table 2.

Our results have been reproduced by several groups. Wholey et al., in a global registry that includes the outcomes of 5210 cases of CAS from 24 centers around the world, reported a technical success rate of 98.4%. The overall 30-day event rate (all-strokes/deaths) was 5.07%. The majority of these patients were treated without the advantage of distal protection.

**Stent restenosis:** Of the first 225 successfully stented patients, follow-up carotid angiography was performed in 121, and carotid ultrasound in 29 patients. Of these, restenosis (defined as 50% diameter narrowing) developed in 8 (5.3%) patients. Only 4 of these patients (2.7%) had restenosis which warranted repeat intervention. Restenosis of stents in the carotid artery can be easily treated with repeat balloon dilatation. Similar rates for restenosis (6-month restenosis rate of 2%) were reported by Wholey et al. in the global registry. Furthermore, the late (>1 year) luminal loss following CAS has been shown to be favorable.

**Late outcome:** Systematic follow-up of 528 patients (99.6%) with 604 successfully stented vessels at a mean of 17±12 months (range 12–55 months) was obtained. There was an incremental 3.2% incidence of fatal and nonfatal stroke beyond 30 days. Freedom from fatal and nonfatal stroke at 3 years was 88%±2% and freedom from ipsilateral nonfatal stroke and all-fatal stroke was 92%±1%.

These results compare very favorably with those seen in the NASCET trial.

**Future Directions**

It is now evident that experienced operators can perform CAS with low complication rates. As with CEA, poor outcomes from CAS may result from poor technical skills and experience. In our view, the most successful results can be attained through collegial collaboration between the various vascular disciplines. There is an urgent need to train endovascular specialists who wish to perform this procedure. The coming years should be focused on education and technical training through symposia, workshops and live demonstration courses. There is also an ongoing need to improve the equipment available for CAS. Often, technical problems are attributed to the inadequacy of currently available devices. There is a need for lower-profile stent delivery systems, better access sheaths and specially designed guidewires and balloons. It is likely that a variety of different stent designs will be required for optimal treatment of anatomical variations of the bifurcation of the carotid artery.

Despite optimal antiplatelet therapy, some patients develop neurological events. These invariably occur during the procedure, occasionally within 1–2 hours and very rarely within the 4 weeks following the procedure. Obstructive carotid artery lesions are known to contain friable thrombotic and atherosclerotic components which can embolize during intervention and are responsible for the majority of the neurological events during CAS. This has been demonstrated in an ex vivo human carotid artery model by Ohki et al. as well as by several transcranial Doppler studies during CAS. Embolization can occur from aggressive guidewire manipulation, balloon dilatation (particularly larger peripheral balloons), during stent deployment and post-stent dilatation. The major challenge from a technical perspective has been the development of “distal protection devices” (Fig. 1) which reliably prevent any particulate matter released during CAS from embolizing to the brain. A number of “distal protection” strategies are currently being evaluated for their efficacy in minimizing the risk of embolic neurological events.

Three approaches are under investigation, all of which provide distal protection during the three critical stages of the carotid intervention: predilatation, stent deployment and postdilatation. Each of these strategies has its inherent advantages and limitations. One approach, first proposed by Vitek et al. and later pioneered by Jacques Théron, involves the use of a distal occlusion balloon which interrupts flow during critical maneuvers likely to release emboli. The column of blood containing embolic material is then aspirated prior to deflating the balloon. Théron reported an impressive reduction of embolic complications from 28% to 2% using this technique. Théron’s concept has now been refined with more advanced technology and similar favorable outcomes have been reported. The second approach involves reversing the flow within the ICA. This is achieved by either occluding the CCA and diverting the blood into the external carotid artery (ECA)—Kachel technique—or by simultaneously occluding the ipsilateral CCA and the ECA, diverting the blood into the guiding catheter which is externally connected to the contralateral femoral vein (Parodi technique). While these two approaches, especially the latter, are advantageous in tortuous arteries, they may not be suitable for the 5%–10% of patients with poor contralateral circulation such as incomplete circle of Willis, who do not tolerate prolonged carotid artery occlusion or flow reversal. The third approach involves the deployment
of an atraumatic embolic filter which is placed prior to definitive lesion dilatation and removed after completion of stent positioning and expansion. The filter has the advantage of providing constant cerebral perfusion, thereby allowing more time for careful and precise intervention of the lesion. Currently available devices are deployed and retrieved on a 0.014" or 0.018" shaft which serves as the guidewire for the balloons and stent delivery system. This approach is limited by the high profile of the currently available filter systems which are difficult to use if the vessel is tortuous. Preliminary data on filter protection are also encouraging, and large clinical trials are currently in progress. Cerebral protection devices have the potential to greatly enhance the safety of CAS and, when available, they will extend this specialized, less invasive approach to the treatment of carotid artery stenoses to community-based interventionalists.

For CAS to attain acceptance as a less traumatic, safe and effective alternative to CEA, it must be validated in a randomized controlled trial. One such trial—the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)—has been completed and a second larger NIH-sponsored study is planned—Carotid Revascularization Endarterectomy Versus Stent Trial (CREST). The CAVATAS, a prospective randomized controlled trial, was conducted in Great Britain through a collaborative effort between neurologists, radiologists and vascular surgeons. In general, the trial included a high-risk, symptomatic population of patients with high-grade carotid artery stenosis. Inclusion criteria were much broader than those of the NASCET trial and, accordingly, this study represents the first prospective evaluation of CEA in higher-risk patients with independent neurological assessment. The study was undertaken at large regional centers in Britain by experienced vascular surgeons. In contrast, the radiologists—stent operators—involved in the trial were operating within their learning curves for carotid intervention. Approximately 20% of the patients actually received stents (usually for "bail-out" application). In addition, the stenting approach in this trial was suboptimal, inferior stents and large-profile peripheral balloons were used, and the technical approach was employed without a guiding sheath using 0.035" wires. Despite these differences in operator experience and the relative maturity of the techniques, both early and late outcomes were similar. The 30-day combined rates of major stroke and death were approximately 6% in both groups and the 2-year neurological outcomes were identical.

The CREST, a randomized controlled trial of CEA versus CAS, plans to recruit 2500 patients with symptomatic stenosis (>50% diameter narrowing, NASCET angiographic criteria). Primary end-points will be the incidence of death, any stroke and myocardial infarction at 30 days, and the incidence of ipsilateral stroke at 4 years after the procedure. The credentials of both surgeons and endovascular interventionists are being rigorously evaluated to ensure that the trial is conducted according to the highest standards.
References


Role of Thrombolytic Therapy for Stuck Prosthetic Valves: A Serial Echocardiographic Study

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Background: Thrombotic occlusion of a prosthetic valve continues to be an uncommon but serious complication. Intravenous thrombolytic therapy has been proposed as an alternative to surgical treatment, but only in critically ill patients.

Methods and Results: Forty-one consecutive patients presenting with 48 episodes of prosthetic valve thrombosis (44 mitral and 4 aortic) were treated with thrombolytic therapy under serial echocardiographic guidance. There were 14 male and 27 female patients. The anticoagulation status was inadequate in 89.6% of episodes. Atrial fibrillation was present in 47.9% of episodes. The prostheses involved in these episodes were tilting disc in 45, bileaflet in 2, and ball and cage type in 1. The Sorin prosthetic valve was the most commonly involved. The time interval between valve replacement and thrombosis ranged from 1 month to 108 months (mean 20.4±20.6 months). Patients were in New York Heart Association functional class III in 47.9% and in class II in 43.9% of episodes. Thrombolytic agents used were streptokinase and urokinase in 44 and 4 episodes, respectively. The mean duration of thrombolytic therapy was 27.9±15.0 hours and the overall success rate was 87.5%. Patients developed peripheral embolism with almost complete recovery in 5 episodes while significant bleeding that required termination of thrombolytic therapy was observed in 2 episodes. Redo valve replacement was done in 3 episodes because these patients did not improve on thrombolytic therapy (all 3 cases were of recurrent prosthetic valve thrombosis and were found to have pannus peroperatively). Three patients died during thrombolytic therapy because of persistent heart failure. Six patients experienced a total of 13 episodes of recurrent prosthetic valve thrombosis including index episodes (rethrombosis in 5, re-rethrombosis in 1). They were treated with repeated thrombolysis with a success rate of 76.92%. The mean duration of thrombolytic therapy in these episodes was 36.1±14.0 hours.

Conclusions: In patients with prosthetic valve thrombosis, intravenous thrombolysis guided by echocardiography is a safe and effective method that may expand the indications for nonsurgical treatment of prosthetic valve thrombosis. By using serial echocardiography, the duration of thrombolytic therapy can be tailored to the patient's requirement for normalization of valve hemodynamics. (Indian Heart J 2001; 53: 451–457)

Key Words: Thrombolysis, Prosthetic valve thrombosis, Echocardiography

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Methods

Patient population: Forty-one consecutive patients admitted to the intensive care unit of our institute between July 1994 and June 2000 with PVT were included. All the patients included in the study had clinical and echocardiographic evidence of prosthetic valve dysfunction (thrombotic) and no contraindication for TLT. The clinical criteria of prosthetic valve obstruction were taken as recent onset significant dyspnea, orthopnea and/or paroxysmal nocturnal dyspnea, and embolic episode, associated with diminished or absent prosthetic valve clicks with or without audible stenotic or regurgitant murmurs across the prosthetic valve.10 The echocardiographic criteria of prosthetic valve obstruction in the mitral position were taken as a calculated mitral valve area of less than 1.6 cm² with an associated end-diastolic gradient >10 mmHg.11 In the aortic position, a peak systolic gradient >50 mmHg was considered abnormal for valves ≥20 mm in size.12

Clinical evaluation and basal investigations: All patients underwent detailed clinical evaluation with special emphasis on diminished prosthetic valve sounds, murmur of recent onset, any evidence of pulmonary venous hypertension, pulmonary arterial hypertension and systemic embolism. Basal routine investigations, which included hemogram, biochemical tests, prothrombin time with International Normalized Ratio (INR), electrocardiography and chest X-ray were also carried out. Adequacy of anticoagulation was defined according to the American Heart Association guidelines.13

Echocardiographic evaluation: Detailed echocardiographic evaluation including transesophageal echocardiography was done using ATL Ultramark®-9 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA, USA) and HP sonos 5500 ultrasound system (Hewlett Packard, Massachusetts, USA). Each patient was carefully interrogated echocardiographically for the presence of any clot and/or pannus.14 Two-dimensional echocardiography was done with special emphasis on looking for opening excursion and completeness of closure of the prosthetic valve and its beat-to-beat variability, if any. The sharpness of opening and closing angles was evaluated by M-mode echocardiography. Doppler echocardiography was done to measure the pressure gradients across the prosthesis.15 The prosthetic valve area was calculated using pressure half-time16 and/or continuity equation, and right ventricular systolic pressure was calculated using tricuspid regurgitation velocity. Cardiac Doppler measurements included an average of three cardiac cycles in patients with sinus rhythm and an average of five cardiac cycles in those with atrial fibrillation. Color flow imaging was done to look for the presence of any regurgitation across the prosthesis. Regurgitation was graded according to previously defined criteria.17 All echocardiographic recordings were taken by two independent observers, and a third one was taken in case of any discrepancy.

Thrombolysis: Thrombolytic therapy was considered for patients fulfilling the criteria of PVT with no contraindication for TLT. Informed consent was taken in each case. Streptokinase (Streptase; Hoechst Marion Roussel, Frankfurt, Germany) or urokinase (Urokinase; TTK Pharmaceutical, Chennai, India) were used as agents for thrombolysis. Streptokinase was given in a loading dose of 2 50 000 units over 30 minutes, followed by an infusion of 1 00 000 units/hour. Hydrocortisone was administered (100 mg intravenously) before the initiation of TLT with streptokinase. An infusion of urokinase was given at a dose of 4400 IU/kg/hour. In addition, all patients received the conventional symptomatic therapy, which included diuretics. The patients were monitored 2-hourly for symptomatic improvement, signs of peripheral embolization and audibility as well as character of prosthetic valve sounds. Serial transthoracic echocardiographic examination was done at 12-hour intervals after the start of TLT. The end-point of therapy was taken as near-normalization of Doppler echocardiographic transvalvular gradients according to previously defined normal values,17 along with clinical improvement. Death of the patient, clinical deterioration during thrombolytic infusion, or lack of improvement in objective measurements even after 72 hours of thrombolytic infusion were regarded as failure of therapy. All patients received heparin infusion at a rate of 1000 units/hour after TLT for a variable period of time until adequate anticoagulation was achieved with nicoumalone or warfarin sodium. In addition, all patients received aspirin 150 mg per day from the day of admission.

Statistical analysis: Continuous variables are presented as mean±standard deviation and compared using paired Student’s t test. Categorical variables are expressed as percentages and analyzed by the Z test. Differences were considered statistically significant if the p value was <0.05.

Results

Demographic profile: Over a period of 72 months (July 1994 to June 2000), a total of 1720 valve replacements
were done in 1566 patients (707 male, 859 female) in our center [Sorin 946 (55%), Medtronic Hall 564 (32.7%), Starr–Edward 164 (9.53%) and St Jude 46 (2.67%)]. During this period, 41 patients with mechanical prosthetic valve replacement presented with 48 episodes of PVT in our hospital. The rate of PVT was highest for Sorin (4.5%), followed by St Jude (2.17%), Medtronic Hall (0.35%), and Starr–Edward (0.06%) prostheses (Table 1). There was female preponderance with a male/female ratio of 14/27. The age of the patients ranged from 13 to 54 years (mean age 33.8±9.3 years). Mitral valve prostheses were involved in 44 episodes and aortic valve prostheses in only 4 episodes of PVT. Both in the mitral as well as in aortic position, Sorin valve prosthesis was the most commonly involved. There were only 2 patients with double valve replacement (DVR) presenting with PVT; mitral prosthesis was involved in one and aortic in the other.

Clinical profile: The interval from surgery to time of presentation varied from 1 month to 108 months (mean duration 20.4±20.6 months). Most of these episodes (n=35, 72.91%) occurred within two years of operation (within 12 months: 45.83%; 13–24 months: 27.08%; after 24 months: 27.08%). The mean duration of symptoms was 10.85±12.57 days. Atrial fibrillation was present in 23 (47.9%) episodes (all with mitral PVT). At the time of diagnosis of PVT, only 5 (10.41%) patients had adequate anticoagulation (Table 1).

The commonest clinical presentation (n=45, 93.75%) was subacute pulmonary edema. Isolated embolism was the clinical presentation in 2 (4.16%) episodes and cardiogenic shock in 1 (2.08%). All the patients of PVT, except those presenting with an embolic event, showed absence or muffling of prosthetic valve sounds. The majority (n=43, 89.6%) also had associated systolic or diastolic murmur of recent onset.

Echocardiographic profile: The diagnosis of PVT was confirmed by echocardiography including transesophageal echocardiography. Two-dimensional echocardiography showed diminished excursion of the disc in all cases of tilting disc or bileaflet disc prostheses, and decreased movement of the ball in cases of ball and cage type prostheses. On M-mode examination, all the patients had blunted opening and closing angles in cases of tilting disc prostheses. Doppler examination revealed significant pressure gradients across the prostheses in all episodes. In the majority of episodes of mitral PVT (n=39, 88.6%), there was associated mitral regurgitation at the time of presentation [mild (grades I and II) in 36, moderate (grade III) in 3], while in all the episodes of aortic PVT there was associated aortic regurgitation [mild (grade III) in 3, severe (grade IV) in 1]. Pulmonary arterial hypertension (PAH) was present in all episodes of mitral PVT (mild in 1, moderate in 20, and severe in 23 patients). The average systolic pulmonary arterial pressure in patients with mitral PVT was 70.7±14.5 mmHg (range 48–120 mmHg). In all episodes of mitral PVT, patients had severe stenosis of the prostheses at the time of presentation (mean valvular area was 0.78±0.11 cm²) (Table 2).

Efficacy of thrombolysis: Streptokinase was the commonly used agent (in 91.66% of episodes), while urokinase was used in only 4 (8.34%) episodes, all in patients with recurrent PVT in whom streptokinase had been used previously (Tables 2 and 3). The mean duration of streptokinase infusion was 26.5±13.77 hours, ranging from 11 to 72 hours. The duration of infusion was longer in episodes of mitral PVT (29.0±15.1 hours) compared to those in aortic PVT (16.0±5.23 hours). The mean duration of urokinase infusion was 34.0±25.6 hours, ranging from 16 to 72 hours. Thrombolytic therapy was successful in a total of 42 (87.5%) episodes. The success rate was slightly higher for episodes of mitral PVT (39/44, 88.6%) compared to those of aortic PVT (3/4, 75%). After successful

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**Table 1. Demographic profile and clinical characteristics of 48 episodes of prosthetic valve thrombosis in 41 patients**

<table>
<thead>
<tr>
<th></th>
<th>All episodes of PVT (n=248)</th>
<th>Mitral PVT (n=44)</th>
<th>Aortic PVT (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>33.8±9.29</td>
<td>33.8±9.6</td>
<td>33.0±4.55</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>14/27</td>
<td>12/25</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>Prosthesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorin</td>
<td>43 (89.58)</td>
<td>40 (90.9)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Medtronic Hall</td>
<td>2 (4.16)</td>
<td>2 (4.54)</td>
<td>-</td>
</tr>
<tr>
<td>St Jude</td>
<td>1 (2.08)</td>
<td>1 (2.27)</td>
<td>-</td>
</tr>
<tr>
<td>Carbomedics</td>
<td>1 (2.08)</td>
<td>1 (2.27)</td>
<td>-</td>
</tr>
<tr>
<td>Starr–Edward</td>
<td>1 (2.08)</td>
<td>-</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Duration of symptoms (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.85±12.57</td>
<td>11.11±13.04</td>
<td>8.0±5.03</td>
</tr>
<tr>
<td><strong>Duration from date of surgery (months)</strong></td>
<td>20.4±20.6</td>
<td>19.1±16.6</td>
<td>34.5±49.2</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>23 (47.9)</td>
<td>23 (52.7)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Anticoagulation status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>41 (85.41)</td>
<td>38 (86.36)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Adequate</td>
<td>5 (10.41)</td>
<td>4 (9.09)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Stopped</td>
<td>2 (4.16)</td>
<td>2 (4.54)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mode of presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>45 (93.75)</td>
<td>41 (93.2)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>21 (43.75)</td>
<td>19 (43.18)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>23 (47.9)</td>
<td>21 (47.72)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>1 (2.08)</td>
<td>1 (2.27)</td>
<td>-</td>
</tr>
<tr>
<td>Embolism</td>
<td>2 (4.16)</td>
<td>2 (4.54)</td>
<td>-</td>
</tr>
<tr>
<td>Shock+Dyspnea</td>
<td>1 (2.08)</td>
<td>1 (2.27)</td>
<td>-</td>
</tr>
<tr>
<td>Decreased prosthetic valve sound</td>
<td>46 (95.83)</td>
<td>42 (95.45)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Regurgitant murmur</td>
<td>43 (89.58)</td>
<td>39 (88.6)</td>
<td>4 (100)</td>
</tr>
</tbody>
</table>

PVT: prosthetic valve thrombosis; NYHA: New York Heart Association; Values in parentheses are percentages.
Thrombolysis, there was near normalization of transvalvular gradients and pulmonary arterial pressures with disappearance of regurgitation across the prostheses. Systemic embolism was observed in 5 (10.41%) episodes—2 patients had cerebrovascular embolism with almost full functional recovery, another 2 had peripheral arterial embolization to the right dorsalis pedis with spontaneous complete recovery; 1 patient had both stroke and peripheral embolism after 13 hours of TLT and recovered spontaneously from both events. Only 2 (4.6%) patients developed significant bleeding—TLT was stopped in both of them. One patient developed a large hematoma in the left arm 11 hours after initiation of TLT so that it had to be stopped. Echocardiography showed good opening excursion of the prosthesis with normalization of gradients, and the hematoma was managed conservatively. Another patient developed significant gingival bleeding after 16 hours, forcing termination of TLT. This patient also had good opening excursion of the prosthesis with near normalization of gradients at the time of stopping TLT.

Three (6.25%) patients required redo surgery (mitral valve replacement in all), as they did not show any improvement with TLT even after 72 hours of infusion. Perioperatively, all these patients had pannus associated with thrombus on their prostheses (Fig. 1). Of these 3 patients, 2 improved following redo valve replacement while the third died in the perioperative period because of intractable heart failure.

Four (8.33%) patients died during the study. Three patients died while on TLT (1 patient presented with cardiogenic shock and could receive TLT for only 2 hours; 2 others died of persistent heart failure after 14 and 28 hours of TLT, respectively), while the fourth patient died in the perioperative period.

### Discussion

Prosthetic valve thrombosis is a life-threatening complication, requiring emergency management, usually in the form of thrombectomy or valve replacement.
Recently, TLT has been recommended as an alternative therapeutic modality but only in critically ill patients.\textsuperscript{3,6,9} However, the majority of patients with prosthetic valve thrombosis do not fall into this category. The first series of TLT for left-sided heart valves was reported by Witchitz in 1980.\textsuperscript{7} In five larger series, success rates between 75\% and 100\% have been reported.\textsuperscript{3,6,7,9,12} Our study is one of its kind, wherein consecutive patients with PVT, irrespective of their presentation, were given TLT and followed up with a comprehensive assessment of valve function (clinically and echocardiographically). By using serial echocardiography, the duration of TLT was tailored to the patient’s requirement for normalization of valve hemodynamics. Our results are in agreement with previous studies including Indian ones (Table 4).\textsuperscript{3,6,7,9,12,18,19,20} The overall success rate of TLT was 87.5\%. It is interesting to note that most patients (87.5\%) required TLT for less than 72 hours (an average of 27.9±15.0 hours of infusion being required for the entire group). Thrombolytic therapy was equally successful in all patients irrespective of the New York Heart Association (NYHA) class. In a recently published large series of 110 patients from India, complete hemodynamic response, unaffected by the NYHA class, was seen in 81.8\% of episodes.\textsuperscript{9}

In our series, the total incidence of complications was 27.08\% (13/48 episodes, including an incidence of 10.41\% for embolism). The fear of potential embolism during TLT has restricted the use of TLT for left-sided valve thrombosis. Gupta et al.\textsuperscript{8} had observed embolic episodes in 19.1\% during therapy, while Ledain et al.\textsuperscript{6} reported an incidence of approximately 18\% of systemic embolism during TLT; they attributed these episodes to breaking of the thrombus present on the prostheses. Roudaut et al.\textsuperscript{3} noted peripheral embolism in 22\% of the cases (14/64), of which 4 had lethal cerebrovascular accident and an additional 6 had transient ischemic attacks. The incidence of peripheral embolism is consistently higher (18\%–22\%) in western series\textsuperscript{6,7} compared to Indian ones (2.8\% in a series by Reddy et al.,\textsuperscript{19} 12\% in the series by Vasan et al.,\textsuperscript{12} and 10.41\% in the present study). The possible reason for the difference might be that the study populations in the western series were elderly (mean age around 50 years v. 33.8 years in the present study). Secondly, the majority of patients in the western series were in atrial fibrillation. The incidence of atrial fibrillation was 82.14\% in the series by Vitale et al.,\textsuperscript{3} 63\% in the study by Miller et al.,\textsuperscript{21} and 53\% in a series by Ozkan et al.\textsuperscript{22} Only a few western studies have reported an incidence less than ours.\textsuperscript{14} Hence the likelihood of a clot in the left atrium is higher, with the added risk of embolization once the valve opens. Since transesophageal echocardiography was not performed in these studies, this theory cannot be confirmed. Thus it is possible that the incidence of systemic embolism in our study population is not as high as reported earlier.

Rethrombosis is the most important complication during follow up, reported to occur in 12\%–24\% of patients after variable follow-up intervals.\textsuperscript{3,6,8,9,21} In our series, 6 patients experienced a total of 13 episodes of recurrent PVT including the index episode (2.2\% patients had rethrombosis while 2.4\% patients had re-rethrombosis). Repeat TLT was given on 7 occasions of which 4 were successful. The efficacy of TLT was similar in previous reports.\textsuperscript{3,19,24} The proposed mechanisms of recurrent PVT are inadequate anticoagulation and pannus formation.\textsuperscript{19,25,26} In our study, anticoagulation was inadequate in 9 (69.23\%) episodes while pannus was found in 3 (23.07\%) episodes and confirmed during surgery in all 3 cases.

Until recently, surgical intervention was the only modality of treatment for PVT. However, the reported mortality is highly variable, ranging from 0\% to 44\%,\textsuperscript{25,26} with an average mortality of 8\%–10\%. This variation is possibly related to the patient’s characteristics at inclusion. Patients in a relatively stable condition have lesser mortality.\textsuperscript{25} The reported immediate mortality with TLT is lower, ranging from 0\% to 17\%.\textsuperscript{3,8,12} In our study, the immediate mortality on TLT was 7.46\% (3/41). Rethrombosis remains the major problem, even with surgery, with an incidence ranging from 1\% to 5\% with thrombectomy and debridement.\textsuperscript{15,26,27} Another important consideration, often overlooked, is the financial burden of a second operation, more so in developing countries. In fact, we initiated TLT as first-line therapy in PVT at our center because most of the patients could not afford a repeat operation, and found it to be cost-effective.

Conclusions: In this series, successful intravenous thrombolysis for PVT was achieved with a low risk of...
Table 4. Indian studies on thrombolytic therapy in prosthetic valve thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/episodes</th>
<th>Mean age (years)</th>
<th>Sex (M/F)</th>
<th>Prosthesis</th>
<th>Duration of symptoms (days)</th>
<th>NYHA class II/III/IV</th>
<th>Inadequate ATC</th>
<th>AF</th>
<th>TLT agents</th>
<th>Infusion (hours)</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasan et al. (1992)</td>
<td>16/16</td>
<td>40.8±13.6</td>
<td>6/10</td>
<td>Bjork-Shiley</td>
<td>37.6±51.8</td>
<td>4/4/8</td>
<td>31.05%</td>
<td>25.0%</td>
<td>STK</td>
<td>42.5±22.7</td>
<td>100.0%</td>
</tr>
<tr>
<td>Rajashekar et al. (1994)</td>
<td>12/13</td>
<td>32.5±12.9</td>
<td>5/7</td>
<td>Medtronic Hall</td>
<td>24.7±31.6</td>
<td>5/4/4</td>
<td>34.46%</td>
<td>41.67%</td>
<td>STK</td>
<td>20.5±11.2</td>
<td>92.0%</td>
</tr>
<tr>
<td>Reddy et al. (1994)</td>
<td>38/44</td>
<td>32.0±12.0</td>
<td>20/18</td>
<td>Carbomedics</td>
<td>NA</td>
<td>0/11/33</td>
<td>70.0%</td>
<td>34.6%</td>
<td>STK/UK</td>
<td>88.6%</td>
<td>88.0%</td>
</tr>
<tr>
<td>Agarwal et al. (1997)</td>
<td>42/42</td>
<td>NA</td>
<td>18/24</td>
<td>St Jude</td>
<td>NA</td>
<td>8/10/24</td>
<td>62.5%</td>
<td>41.3%</td>
<td>STK/UK</td>
<td>88.0%</td>
<td>88.0%</td>
</tr>
<tr>
<td>Gupta et al. (1999)</td>
<td>110*</td>
<td>35.4±10.8</td>
<td>52/58</td>
<td>Sorin</td>
<td>14****</td>
<td>25/51/34</td>
<td>38.0%</td>
<td>41.5%</td>
<td>STK/UK</td>
<td>91.8%</td>
<td>91.8%</td>
</tr>
<tr>
<td>Present study</td>
<td>41/48</td>
<td>33.8±9.29</td>
<td>14/27</td>
<td>Starr-Edwards</td>
<td>10.8±12.5</td>
<td>21/23/2</td>
<td>31.8%</td>
<td>47.9%</td>
<td>STK/UK</td>
<td>87.5%</td>
<td></td>
</tr>
</tbody>
</table>

NA: not available; NYHA: New York Heart Association; ATC: anticoagulation; AF: atrial fibrillation; TLT: thrombolytic therapy; STK: streptokinase; UK: urokinase; CVA: cerebrovascular accident

*Details of episodes of recurrent thrombosis not available; **Standard deviation not mentioned; ***Mean duration of symptoms not mentioned; ****Median duration

complications and a high rate of success. Thrombolytic treatment was equally effective in PVT of both the mitral and aortic valves and in all types of prostheses. We believe that intravenous infusion of thrombolytics, monitored thereafter by echocardiography, is a safe and effective method of nonsurgical treatment of PVT. Serial echocardiography helps in tailoring the duration of TLT required for normalization of valve hemodynamics.

References

Carotid Intima–Media Thickness as an Independent Predictor of Coronary Artery Disease

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Department of Non-Invasive Cardiology, MGM New Bombay Hospital, New Mumbai

Background: Recently, considerable attention has been directed at the wall thickness of the carotid arteries as an early marker of atherosclerotic disease and in the prediction of clinical coronary events and coronary artery disease. The present study evaluated the association of carotid artery intima–media thickness in the prediction of coronary artery disease in a western Indian population.

Methods and Results: Carotid artery intima–media thickness was measured with a B-mode scan in an ongoing study of 266 patients, who were further subdivided into 4 subgroups: those with non-insulin dependent diabetes mellitus; hypertension; diabetes mellitus with hypertension; and those without diabetes or hypertension (labeled as controls). The maximal intima–media thickness greater than 0.8 mm at the far wall of the common carotid artery, excluding raised lesions and plaques, was selected as the highest value for comparison. The subgroups were further divided into those with and without apparent coronary artery disease. A statistically significant intima–media thickness greater than 0.8 mm was observed in 59.2% of the subjects with coronary artery disease as against 40.8% in those without the disease on univariate analysis. A higher incidence of intima–media thickness of more than 0.8 mm was observed in all subgroups with coronary artery disease as against those without the disease, which was most marked in the hypertensive group (22.2% v. 3.6%) and contributed to the increased arterial thickness in diabetics with concomitant hypertension. Multivariate regression analysis revealed carotid artery intima–media thickness to be associated with coronary artery disease with an odds ratio of 2.40.

Conclusions: Carotid artery intima–media thickness is a simple, noninvasive and reproducible clinical tool to evaluate atherosclerosis and predict coronary artery disease in Indian subjects. Prospective studies in a larger number of subjects, particularly in those undergoing coronary angiography, will help in establishing the role of this technique. (Indian Heart J 2001; 53: 458-462)

Key Words: Carotid arteries, Coronary disease, Ultrasonography
Methods

A total of 266 randomly selected patients, both hospitalized as well as outpatient, were studied. Informed consent was obtained from the subjects (166 males and 100 females). Subjects were divided into two groups: with CAD (99 subjects) and without CAD (167 subjects). They were further subdivided into 3 subgroups in context to risk stratification for CAD: non-insulin dependent diabetes mellitus (78 subjects); hypertension (74 subjects); and diabetes with concomitant hypertension (63 subjects). Subjects not belonging to these categories were termed as controls. The 51 subjects labeled as controls were randomly selected and included those with risk factors such as dyslipidemia, smoking and obesity. The ages of the subjects ranged from 36 to 64 years and their mean age was 50.5 years. Baseline characteristics of the subjects in the groups with and without CAD are shown in Table 1 and the baseline characteristics of the various subgroups in context to the control cases are shown in Table 2.

Ultrasonographic scanning of the carotid arteries was performed in the supine position with the neck extended, using a high-frequency imaging probe (7.5 mHz) with a Hewlett-Packard scanner, at a depth of 2 cm, as the carotid vessels are relatively superficial. The carotid vessels were followed from the clavicular head cephalad to their bifurcation and 3–4 cm of the proximal internal and external carotid arteries were studied. The IMT was measured at end-diastole at 4 different points in the far wall of both the CCAs. The maximum IMT and not the mean was taken into consideration for calculating the results. Raised lesions and carotid plaques were excluded while calculating the maximum IMT, as the study was specifically aimed at correlating the IMT at sites free of plaques although conventionally, plaques have been included in most studies. Age-adjusted IMT values >0.8 mm were labeled as the higher quartile for correlating the association between IMT and the prevalence of CAD. Interobserver variability was 0.034 mm and intraobserver variability 0.029 mm. Films were recorded in all subjects for documentation.

Coronary artery disease was diagnosed by clinical presentation, with electrocardiography, symptom-limited exercise stress test, Doppler echocardiography and coronary angiography documentation, when feasible. Of the 99 subjects with CAD, 47 had evidence of myocardial infarction or acute coronary syndrome, 22 had evidence of CAD on coronary angiography, and 30 had ECG, stress test and echocardiographic manifestations suggestive of CAD.

Clinical examination included blood pressure measurement, cardiovascular examination, anthropometric measurements and body mass index. Biochemical assessment included fasting and postprandial blood sugar levels, glycated hemoglobin, urine for microalbumin, and

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CAD (n=99)</th>
<th>Non-CAD (n=167)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.8±8.7</td>
<td>48.2±8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65 (65.7)</td>
<td>101(60.5)</td>
<td>&lt;0.400</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>31 (31.3)</td>
<td>15 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>18 (18.2)</td>
<td>56 (33.5)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>55 (51.5)</td>
<td>86 (55.5)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5±3.37</td>
<td>26.0±3.36</td>
<td>&lt;0.245</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>124.3±56.7</td>
<td>114.5±48.7</td>
<td>&lt;0.140</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>208.4±43.4</td>
<td>205.4±46.8</td>
<td>&lt;0.567</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>126.9±39.2</td>
<td>122.5±44</td>
<td>&lt;0.414</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>41.7±7.7</td>
<td>42.9±7.4</td>
<td>&lt;0.211</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>165.6±80.1</td>
<td>167.1±103.6</td>
<td>&lt;0.899</td>
</tr>
<tr>
<td>Cholesterol–HDL ratio</td>
<td>5.07±1.1</td>
<td>4.85±1.1</td>
<td>&lt;0.130</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dl)</td>
<td>1.27±0.34</td>
<td>1.36±0.39</td>
<td>&lt;0.064</td>
</tr>
<tr>
<td>Apoliprotein B (mg/dl)</td>
<td>1.41±0.40</td>
<td>1.27±0.48</td>
<td>&lt;0.016</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Diabetes and hypertension</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.1±9.9</td>
<td>50.4±8.7</td>
<td>48.9±8.9</td>
<td>52.8±7.5</td>
<td>&lt;0.159</td>
</tr>
<tr>
<td>Male (%)</td>
<td>34 (66.7)</td>
<td>47 (60.3)</td>
<td>52 (70.3)</td>
<td>33 (52.4)</td>
<td>&lt;0.152</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>11 (21.6)</td>
<td>9 (11.5)</td>
<td>15 (20.3)</td>
<td>11 (17.5)</td>
<td>&lt;0.406</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.02±2.73</td>
<td>24.97±2.60</td>
<td>26.75±3.34</td>
<td>26.63±4.21</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>85.62±14.4</td>
<td>151.7±65.3</td>
<td>87.17±15.7</td>
<td>137.3±34.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>197.38±34.4</td>
<td>215.35±50.7</td>
<td>194.47±48.3</td>
<td>215.68±38.9</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>120.1±36.3</td>
<td>126.1±47.6</td>
<td>115.06±43.4</td>
<td>135.3±36.2</td>
<td>&lt;0.040</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>41.33±7.4</td>
<td>43.6±7.7</td>
<td>41.9±7.8</td>
<td>42.4±7.0</td>
<td>&lt;0.035</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>159.2±87</td>
<td>162.4±102.6</td>
<td>162.5±82.3</td>
<td>176±107.2</td>
<td>&lt;0.794</td>
</tr>
<tr>
<td>Cholesterol–HDL ratio</td>
<td>4.88±1.1</td>
<td>5.09±1.3</td>
<td>4.69±1.0</td>
<td>5.05±1.0</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dl)</td>
<td>1.32±0.31</td>
<td>1.27±0.37</td>
<td>1.37±0.43</td>
<td>1.35±0.35</td>
<td>&lt;0.037</td>
</tr>
<tr>
<td>Apoliprotein B (mg/dl)</td>
<td>1.25±0.36</td>
<td>1.40±0.52</td>
<td>1.21±0.41</td>
<td>1.43±0.47</td>
<td>&lt;0.012</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages
comprehensive lipid profile inclusive of apolipoproteins A1 and B. Results of the biochemical parameters in all the subgroups have been shown in Tables 1 and 2.

**Statistical analysis:** Chi-square and odds ratio with confidence interval (CI) and multivariate regression analysis were computed with the SPSS statistical software package (Version 10); p values <0.05 were considered significant.

**Results**

The relationship between CAD and IMT is shown in Table 3 and Fig. 1. Among subjects with evidence of CAD, 59.2% had IMT values exceeding 0.8 mm as compared to 40.8% in those without obvious evidence of CAD, which was highly significant (p<0.001) on univariate analysis. The odds ratio for an arterial thickness exceeding 0.8 mm was 3.04 in those with CAD as against those without obvious CAD, making it an important marker for preclinical and clinical CAD.

The importance of increased arterial thickening in high-risk subgroups is shown in Table 4, with an additive adverse effect of concomitant hypertension in subjects with diabetes mellitus with or without CAD, as reflected by a higher incidence of IMT exceeding 0.8 mm. On subgroup analysis (Table 5), IMT exceeding 0.8 mm had the strongest correlation for CAD in subjects with hypertension (with an incidence of 22.2%) as against those without CAD (only 3.6%), although all high-risk subgroups showed a positive correlation as illustrated in Fig. 2. Carotid artery IMT values remain in the higher quartile in subjects with hypertension.

**Table 3. CAD–IMT crosstabulation**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients without CAD</th>
<th>Number of patients with CAD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT &lt;0.8 mm</td>
<td>147 (67.4)</td>
<td>70 (32.6)</td>
<td>217 (100)</td>
</tr>
<tr>
<td>IMT &gt;0.8 mm</td>
<td>20 (40.8)</td>
<td>29 (59.2)</td>
<td>49 (100)</td>
</tr>
</tbody>
</table>

Pearson Chi-square: 12.4, p<0.001; Odds ratio: IMT <0.8 mm or IMT >0.8 mm for CAD=3.0 (95% CI 1.6–5.7)

**Table 4. IMT subgroup crosstabulation**

<table>
<thead>
<tr>
<th></th>
<th>Number of control patients</th>
<th>Number of patients with NIDDM</th>
<th>Number of patients with hypertension</th>
<th>Number of patients with NIDDM+HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT &lt;0.8 mm</td>
<td>47 (92.2)</td>
<td>64 (82.1)</td>
<td>68 (91.9)</td>
<td>38 (60.3)</td>
</tr>
<tr>
<td>IMT &gt;0.8 mm</td>
<td>4 (7.8)</td>
<td>14 (17.9)</td>
<td>6 (8.1)</td>
<td>25 (39.7)</td>
</tr>
</tbody>
</table>

Pearson Chi-square: 27.9, p<0.001; NIDDM: non-insulin dependent diabetes mellitus; IMT: intima–media thickness; HT: hypertension

**Values in parentheses are percentages**

**Table 5. IMT: without CAD and with CAD for individual subgroups**

<table>
<thead>
<tr>
<th></th>
<th>Number of control patients</th>
<th>Number of patients with NIDDM</th>
<th>Number of patients with hypertension</th>
<th>Number of patients with NIDDM+HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT &lt;0.8 mm</td>
<td>24 (96.0)</td>
<td>46 (85.2)</td>
<td>54 (96.4)</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>IMT &gt;0.8 mm</td>
<td>1 (4.0)</td>
<td>8 (14.8)</td>
<td>2 (3.6)</td>
<td>9 (38.1)</td>
</tr>
<tr>
<td>With CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT &lt;0.8 mm</td>
<td>23 (88.5)</td>
<td>18 (75.0)</td>
<td>14 (77.8)</td>
<td>15 (48.4)</td>
</tr>
<tr>
<td>IMT &gt;0.8 mm</td>
<td>3 (11.5)</td>
<td>6 (25.0)</td>
<td>4 (22.2)</td>
<td>16 (51.6)</td>
</tr>
</tbody>
</table>

Pearson Chi-square: 13.5, p<0.004 for subgroup without CAD; Pearson Chi-square: 12.0, p<0.007 for subgroup with CAD

NIDDM: non-insulin dependent diabetes mellitus; HT: hypertension

**Values in parentheses are percentages**

Fig. 1. Distribution of patients with CAD and without CAD by intima–media thickness.

Fig. 2. Percentage of patients with intima–media thickness above 0.8 mm by groups and subgroups.
and diabetes mellitus, but the incidence increases significantly in the presence of CAD.

Multivariate regression analysis using age-adjusted IMT as a dependent variable and diagnosis (in the context of subgroups), sex, smoking, LDL-cholesterol, HDL-cholesterol, total cholesterol to HDL-cholesterol ratio, apolipoprotein A1 to B ratio and microalbuminuria as independent variables showed a strong association with CAD (p< 0.019, odds ratio: 2.40) (Table 6).

Table 6. Multivariate regression analysis for CAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β</th>
<th>SE</th>
<th>p value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.321</td>
<td>0.318</td>
<td>&gt;0.05</td>
<td>1.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.487</td>
<td>0.407</td>
<td>&lt;0.001</td>
<td>4.4</td>
</tr>
<tr>
<td>Subgroup</td>
<td>-0.083</td>
<td>0.138</td>
<td>&gt;0.05</td>
<td>0.9</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>-0.316</td>
<td>0.431</td>
<td>&gt;0.05</td>
<td>0.7</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>-0.157</td>
<td>0.389</td>
<td>&gt;0.05</td>
<td>0.8</td>
</tr>
<tr>
<td>Total cholesterol to HDL-C ratio</td>
<td>0.003</td>
<td>0.320</td>
<td>&gt;0.05</td>
<td>1.0</td>
</tr>
<tr>
<td>Apo1 to HDL-C ratio</td>
<td>0.498</td>
<td>0.332</td>
<td>&gt;0.05</td>
<td>1.6</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.887</td>
<td>0.376</td>
<td>&lt;0.018</td>
<td>2.4</td>
</tr>
</tbody>
</table>

SE: standard error; LDL-cholesterol: low-density lipoprotein cholesterol; HDL-cholesterol: high-density lipoprotein cholesterol; IMT: intima-media thickness

Discussion

Ultrasonography is a reliable and accurate technique to determine IMT in the superficial arteries. Reproducibility of IMT determination is best in the CCA of healthy subjects and in patients with advanced atherosclerosis.9–12 B-mode ultrasound scan including carotid IMT measurement and peripheral plaque detection may be of clinical value in the screening of patients with CAD.11

The Rotterdam study,14 which involved a 4-year follow-up of almost 8000 patients, showed that there was, in fact, a significantly higher incidence of stroke and myocardial infarction in patients who had increased IMT. Bots et al.,15 in the Rotterdam study showed that the 10-year absolute risk of coronary heart disease rose from 13% to 23.4%, whereas the risk of death within 11.5 years rose from 15% in the lowest quintile to 46% in the highest quintile.

Hodis et al.,16 in a long-term follow-up study, showed that for each 0.03 mm increase per year in carotid artery IMT, the relative risk for nonfatal myocardial infarction or coronary death was 2.2 and the relative risk for coronary events was 3.1. Absolute thickness and progress in thickness predicted risk for a coronary event beyond that predicted by coronary arterial measures of atherosclerosis and serum lipid levels. The B-mode score is at least as useful as other well-known risk factors for identifying patients with CAD.17

The Cardiovascular Health Study Collaborative Research Group18 has recently shown in 4476 subjects without clinical cardiovascular disease followed up over 6 years, that the relative risk for myocardial infarction or stroke for the quintile with the highest IMT as compared with the lowest was 3.87. The present study has also shown a risk estimate of 3.04 for CAD in subjects with an increased IMT. It is a strong independent predictor for new cardiovascular events, even after statistical adjustment for other traditional risk factors. This finding has clinical significance, particularly with regard to the elderly.

This study also shows a significant increase in IMT in the hypertensive population which is consistent with reported studies of greater IMT of the CCA in sedentary and active hypertensives than normotensives.19,20 This is of therapeutic importance in diabetics with concomitant hypertension, as shown in an earlier study.21 Mohan et al.,22 demonstrated an increased IMT in 243 south Indian diabetic and non-diabetic subjects in the Chennai Urban Population Study, and the findings are further confirmed in this study from the western part of the country. Besides the usual conventional risk factors, a significant positive correlation has been shown between plasma homocysteine levels and carotid artery IMT in the context of CAD in the NHLBI Family Heart Study,23 which can have future implications for Indian subjects. Carotid artery IMT exhibits less variability, is associated with cardiovascular risk factors, and increased levels can predict myocardial infarction and stroke. Aggressive management of risk factors can decrease IMT.24

Conclusions: The present study is an example of evidence-based medicine in correlating two vascular beds, coronary and carotid, which share the same atherosclerotic risk factors. Carotid artery IMT—a simple, safe, noninvasive and reproducible method—can be used as a surrogate marker in the prediction of atherosclerosis and CAD, as has been demonstrated. The results can be improved upon and made more precise by increasing the sample size. The present study has some limitations in that it is not a prospective cohort study and a long-term follow-up of subjects without CAD is required to demonstrate the utility of IMT in predicting CAD. Measurement of the mean of maximal IMT in both the CCA and carotid bulb and inclusion of plaques will contribute to a higher IMT and strengthen the results further. The obvious limitation of the study, however, is the lack of angiographic documentation in both the groups.
for the presence of CAD, apart from 69 patients in the group with CAD. This could not be performed because of logistic, ethical and socio-economic reasons. IMT measurement should be included as a diagnostic tool, given the paucity of facilities for invasive techniques in India. This will help in early identification of clinical and preclinical CAD. Finally, long-term follow-up studies from India are required to address the utility of this technique for therapeutic intervention.

Acknowledgments

We gratefully acknowledge the help provided by the Departments of Pathology and Ultrasonography, MGM New Bombay Hospital and Dr DP Singh for the statistical analysis.

References

Lipoprotein (a) and Lipid Levels in Young Patients with Myocardial Infarction and Their First-Degree Relatives

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Department of Cardiology, King George's Medical College, Lucknow

Background: Studies among emigrant Indians have stressed the role of a powerful genetic factor, lipoprotein (a), in the causation of premature coronary artery disease. This study was carried out to assess lipoprotein (a) and lipid levels in 50 consecutive young north Indian patients (age less than 45 years, mean age 39±3.7 years) with myocardial infarction, their first-degree relatives (n=125, mean age 36±16 years), and age- and sex-matched controls (n=50, mean age 34±6.9 years).

Methods and Results: Blood samples for lipid estimation were taken within 24 hours of myocardial infarction and after overnight fasting for twelve hours. Lipoprotein (a) levels were estimated by the ELISA technique using preformed antibodies while lipid levels were estimated by kits using the colorimetric method. All were male patients. The mean lipoprotein (a) level was 22.28±5.4 mg/dl in patients, 13.88±5.19 mg/dl in their first-degree relatives and 9.28±22.59 mg/dl in controls. In addition, it was significantly higher in young patients with myocardial infarction and their relatives as compared to controls (p<0.001 for patients v. controls and p<0.05 for relatives v. controls). There was no significant difference in the levels of total cholesterol and low-density lipoprotein cholesterol among the three groups. High-density lipoprotein cholesterol was significantly lower in young patients with myocardial infarction (30.16±9.45 mg/dl) and their first-degree relatives (33.28±8.45 mg/dl) as compared to controls (46.8±8.04 mg/dl) (p<0.001 for patients v. controls and p<0.01 for relatives v. controls). Triglyceride levels were significantly higher in patients compared to controls (202±76 mg/dl v. 149±82.99 mg/dl, p<0.05). Smoking was more prevalent in young patients with myocardial infarction as compared to controls (44% v. 36%, p<0.05).

Conclusions: Smoking, high lipoprotein (a) and triglyceride levels and low high-density lipoprotein levels may be important risk factors for coronary artery disease in the younger population; also, there is familial clustering of high lipoprotein (a) levels in first-degree relatives of young patients with myocardial infarction. (Indian Heart J 2001; 53: 463–466)

Key Words: Lipoproteins, Myocardial infarction, Coronary disease

Coronary artery disease (CAD) is now a major public health problem in India and is emerging as a major killer. Of all ethnic groups, people of Indian origin have one of the highest incidences of CAD, and diffuse and severe CAD frequently occurs in Indians at an early age. The prevalence of premature CAD in Indians is up to 3 times higher when compared with people of a similar age group in the western world.

One of the most striking characteristics of premature CAD in Indians is a relatively low prevalence of traditional coronary risk factors. Little is known about the pathogenesis of atherosclerosis and CAD in Indians, while belonging to different religious groups with varying cultural backgrounds and living in different geographical regions, share the common problem of high mortality from the disease. Available data suggest the presence of a powerful risk factor unaffected by even maximal modification of lifestyle. Familial aggregation of a number of cardiovascular diseases has long pointed to the possible role of primary genetic factors in their pathogenesis. Many studies in the past have demonstrated that lipoprotein (a) [Lp(a)], a genetically determined lipoprotein, is one of the most powerful and most prevalent independent risk factors for premature CAD.

Because the disease affects Indians in the prime of their lives and careers and has significant socio-economic consequences, there is an urgent need to define the pathophysiological process involved and to look for familial
clustering, so that an intensive program of primary prevention and alteration of modifiable risk factors can be drawn.

Lipoprotein (a) is fully expressed in the first year of life and high levels have almost the same predictive value as a family history of premature CAD. Therefore, “tracking” Lp(a) levels from childhood may be a better option than detecting other dyslipidemias which are not fully expressed until middle age. Keeping the aforementioned objectives in mind, Lp(a) and lipid levels were determined in young patients (<45 years) with myocardial infarction (MI) and their first-degree relatives, and were compared with those of a control population.

Methods

Subjects included in this study were consecutive patients with MI, less than 45 years of age admitted in our hospital during the study period, and their first-degree relatives. All young patients with MI were male. Informed consent of the patients, their relatives and controls was taken before enrollment in the study.

Patients included in the study were less than 45 years of age and admitted with acute myocardial infarction (AMI) which was diagnosed by the presence of at least 2 of 3 criteria, i.e. anginal chest pain of more than 30 minutes' duration; ST segment elevation more than 1 mm above baseline in at least two leads of a standard 12-lead electrocardiogram (ECG); and creatinine kinase and creatinine kinase-MB elevation to at least twice the upper limit of the normal range.

First-degree relatives of these patients, i.e. their brothers, sisters, children and parents were included in the study. The following patients were excluded from the study: patients more than 45 years of age; patients with chronic renal parenchymal disease or nephrotic syndrome; patients with concomitant liver disease; and patients with any disabling terminal disorder. Age- and sex-matched controls with no family history of manifest CAD and their ECGs were normal. Patients, their relatives and controls were subjected to detailed clinical examination with special reference to the concomitant risk factors, i.e. smoking, diabetes, hypertension, obesity and family history of premature CAD.

Blood samples of the patients were taken within 24 hours of MI and after 12-hour overnight fasting. Blood samples of the relatives and controls were also taken after 12-hour overnight fasting. For isolation of plasma, a 10 ml blood sample was centrifuged at 2000 rpm at 4°C for 20 min and aspirated into tubes preflushed with nitrogen. Lipoprotein (a) was isolated by density gradient ultracentrifugation. Isolated Lp(a) was purified by lysine sepharose chromatography and the purity established by gel electrophoresis. Lipoprotein (a) level was estimated by the ELISA method, using preformed antibodies.

Serum concentrations of total cholesterol (TC) and triglyceride (TG) were estimated by the colorimetric method and high-density lipoprotein (HDL) cholesterol was measured by the CHOD–PAP method using Boehringer Mannheim kits. Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula, i.e. LDL-cholesterol = Total cholesterol – [Triglycerides/5 + HDL]

Statistical analysis: All values are expressed as the mean±standard deviation. To see the inter-relationship between two variables, the Pearson Product Movement Correlation Coefficient was used while to test the significance of the correlation, the Student’s t test was used.

Results

The subjects were divided into 3 groups, young patients with MI, first-degree relatives of patients, and age- and sex-matched controls. Lipoprotein (a) level and lipid profile were estimated in 50 patients with MI, 125 first-degree relatives of these patients and in 50 age- and sex-matched controls. Baseline characteristics of the patients, their relatives and controls are shown in Table 1. All patients with MI and controls were male. Smoking was the most prevalent risk factor, present in 44% of young patients with MI as compared to 36% of controls (p<0.05).

Table 1. Demographic profile of the patients, their relatives and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young patients with MI</th>
<th>First-degree relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>50</td>
<td>125</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39±3.71</td>
<td>36±16</td>
<td>34±6.9</td>
</tr>
<tr>
<td>Male</td>
<td>50</td>
<td>87</td>
<td>50</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (20)</td>
<td>6 (5)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (14)</td>
<td>7 (5.6)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (44)</td>
<td>34 (27)</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Truncal obesity</td>
<td>10 (20)</td>
<td>12 (9.6)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>12 (24)</td>
<td>125</td>
<td>Nil</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; CAD: coronary artery disease
Values in parentheses are percentages

Lipoprotein (a) and lipid levels estimated in these groups are shown in Table 2. Distribution of Lp(a) in the 3 groups (Table 3) shows that 30/50 (60%) young patients with MI had Lp(a) levels between 20 and 30 mg/dl, while 101/125 (82.5%) of their first-degree relatives had lower levels (between 10–20 mg/dl). By comparison, 34/50 (68%)
controls had still lower Lp(a) levels (below 10 mg/dl). No patient with MI had Lp(a) levels less than 10 mg/dl. Very high levels of Lp(a) (>30 mg/dl) were found in 5/50 (10%) young patients with MI, 4/125 (3.2%) of their first-degree relatives and none of the controls.

Table 2. Lp(a) and lipid levels in the study and control populations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young patients with MI</th>
<th>First-degree relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>50</td>
<td>125</td>
<td>50</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>22.24±5.4</td>
<td>13.88±5.19</td>
<td>9.28±2.59</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>191.43±44.07</td>
<td>176.93±34.65</td>
<td>173.45±52.21</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>202.00±76.10</td>
<td>153.74±82.92</td>
<td>149.60±82.99</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>118.01±35.31</td>
<td>113.11±32.81</td>
<td>99.05±38.92</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>30.16±9.45</td>
<td>33.28±6.45</td>
<td>46.81±6.04</td>
</tr>
</tbody>
</table>

Lp(a): lipoprotein (a); LDL: low-density lipoprotein; HDL: high-density lipoprotein; mg/dl: milligram per deciliter

Table 3. Lp(a) levels in the study and control populations

<table>
<thead>
<tr>
<th>Lp(a)</th>
<th>Young patients with MI</th>
<th>First-degree relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mg/dl</td>
<td>Nil</td>
<td>12(9.4)</td>
<td>34(68)</td>
</tr>
<tr>
<td>10–20 mg/dl</td>
<td>15(30)</td>
<td>101(82.5)</td>
<td>16(32)</td>
</tr>
<tr>
<td>20–30 mg/dl</td>
<td>30(60)</td>
<td>8(5.43)</td>
<td>Nil</td>
</tr>
<tr>
<td>&gt;30 mg/dl</td>
<td>5(10)</td>
<td>4(2.67)</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Lp(a): lipoprotein (a); MI: myocardial infarction; mg/dl: milligram per deciliter
Values in parentheses are percentages

Statistical comparison of Lp(a) and lipid levels among the 3 groups shows that TC and LDL-cholesterol levels did not differ significantly in the 3 groups (p value not significant). High-density lipoprotein cholesterol was significantly lower in young patients with MI and their first-degree relatives as compared to controls (p<0.001 for patients v. controls and p<0.01 for relatives v. controls). Triglyceride levels were also significantly higher in patients as compared to controls (p<0.05).

Lipoprotein (a) level in patients with MI and their first-degree relatives was significantly higher as compared to controls (p<0.001 and p<0.05 for patients v. controls and relatives v. controls, respectively).

Discussion

As compared to other ethnic groups, prevalence of CAD in the young is much higher in Indians.14 Manifestation of CAD in a more extensive form at a younger age despite a relatively low longitudinal burden of conventional risk factors points to some other risk factors, presumably genetically determined, which predispose our population to an increased risk at a much younger age. If these factors can be identified, preventive measures can be instituted in time.

Prevalence of hypertension (20%) and diabetes mellitus (14%) was not very high in our study population and was similar to the incidence reported in previous studies.15 Smoking was the most prevalent risk factor in young patients with MI. Previous studies have shown familial clustering of CAD and its risk factors.16 However, we do not know whether data from studies done on overseas Indians can be extrapolated to those living in India and Indian data regarding Lp(a) and lipid levels in young patients with MI and their relatives is lacking. In our study, we found that the difference in total- and LDL-cholesterol levels in young patients with MI and controls was statistically insignificant. High-density lipoprotein levels in patients and their first-degree relatives were significantly lower while TG levels were significantly higher in patients as compared to controls (p<0.05). Low HDL-cholesterol and high TG levels in Indians have been reported earlier.17

Lipoprotein (a) is considered to be an independent risk factor for premature18 and multivessel CAD.19 Lipoprotein (a) consists of 2 different components, apolipoprotein (B)-100 which binds to LDL receptors and acts as an atherogenic protein and apolipoprotein (A) which resembles plasminogen and competes with the latter for binding to fibrinogen and fibrin monomer, thus acting as a prothrombotic agent. Thus, Lp(a) functions as a dual pathogen which is highly atherogenic and is also prothrombotic. The mean Lp(a) level in our study was 22.24±5.4 mg/dl in patients, 13.88±5.19 mg/dl in their first-degree relatives and 9.28±2.59 mg/dl in controls. The CADI (Coronary Artery Disease in Asian Indians) study showed that the Lp(a) level in Asian Indians is high. Bhatnagar et al.16 also reported high mean Lp(a) levels among Asian Indians living in the UK and their siblings in India. Shaukat et al.10 found that mean Lp(a) levels were nearly double in sons of Asian Indians (age range 15–30 years) as compared to sons of White parents of similar age 19 mg/dl v. 10 mg/dl). A recent study by Gupta et al.21 showed that TC, LDL-cholesterol, HDL-cholesterol and TG levels were not significantly different in cases of CAD and controls but Lp(a) levels were significantly higher in cases (p<0.04). A study by Gambhir et al.22 reported that low HDL-cholesterol and high Lp(a) levels were independent risk factors for premature CAD. These studies and our data suggest the genetic nature of the Lp(a) trait and clustering of high Lp(a) levels in families of patients with premature CAD.

Conclusions: Our study suggests that smoking, high Lp(a), high TG, and low HDL levels are the most important risk factors for premature CAD.
factors for CAD in the young. First-degree relatives of young patients with MI also show high Lp(a), high TG and low HDL levels. These findings have important preventive and therapeutic implications. Extensive lifestyle modification and therapeutic interventions should begin early and at lower levels of TC and LDL-cholesterol, particularly in persons with a family history of premature CAD and in persons with high Lp(a) levels.

References
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14. Enas EA, Yusuf S, Garg A, Davidson L, Thomas T, Pearson TA. Lipoprotein (a) levels in Indian physicians: comparison with white and black physicians in the USA. Indian Heart J 1994; 46: 1
A Cardiac Evoked Response Algorithm Providing Automatic Threshold Tracking for Continuous Capture Verification: A Single-Center Prospective Study

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Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh

Background: The AutoCapture™ algorithm as implemented in Regency® and Microny® pacemakers (Pacesetter Inc., Sylmar, CA, USA) provides beat-by-beat monitoring of capture based on proper detection of the evoked response, provides high output back-up pulse when loss of capture occurs, performs periodic threshold evaluations and acquires the capture threshold data in a time-based event counter for later retrieval. The safety and efficacy of this algorithm was prospectively evaluated at a tertiary care hospital of north India.

Methods and Results: Fifty-four patients (38 males, mean age 66±13 years) received a ventricular pacemaker model Regency® SC+ with low polarization bipolar lead for high-grade atrioventricular block (n=42) and sick sinus syndrome (n=12). Evoked response and polarization signal were assessed initially at 24 hours postimplant, and follow-up measurements were systematically conducted at week 1 and months 1, 3 and 6. Further evaluation of eligible patients was performed at 6-monthly intervals. Lead implantation parameters were optimum in all patients. At 6 months, the algorithm was functional in 51 patients. The pacing threshold increased to 0.89±0.36 V (p<0.001) in the first month and stabilized thereafter. Significant saving of energy was accomplished by a constant output safety margin of 0.3 V instead of the traditional 100%. While the evoked response signal remained stable throughout the study period, the potential signal increased significantly from 0.6±0.7 mV to 1.0±0.6 mV (p<0.001) in the first month and remained steady subsequently. Back-up pacing in the event of exit block was confirmed in all 25 patients who underwent a 24-hour Holter test. Based on the suggested sense margins, ventricular undersensing was observed in 7 (28%) patients, the majority of whom had competitive cardiac rhythms. An elderly patient with pneumonic illness succumbed to pulmonary embolism at 6 months.

Conclusions: This large single-center experience on AutoCapture demonstrates the success of this algorithm in low-energy ventricular pacing without compromising the patient’s safety. (Indian Heart J 2001; 53: 467-476)

Key Words: Pacemaker, AutoCapture, Heart block

Present-day multiparameter pacemaker programming is sophisticated and time consuming. The industry has provided solutions, incorporating automatic functions into the latest pacemakers that may help to speed up patient follow-up and optimize individual parameter adjustment. The development of an automatic pacemaker algorithm that can independently verify pacemaker capture and determine pacing threshold is likely to provide an added margin of safety and help to prolong longevity of the pacemaker. One such algorithm is the ‘AutoCapture’ which requires detection of an evoked response (ER) following the pacemaker depolarizing stimulus. It is configured to control the effectiveness of each pacing pulse, deliver a back-up pacing pulse, increase the output in case of ineffective pacing and adjust the pulse amplitude every 8 hours to the actual pacing threshold.¹

The recognition of a cardiac ER by the pacemaker is hampered by the polarization voltage at the electrode-tissue interface.² Typically, the peak amplitude of a paced ER is between 5 and 30 mV. The polarization is actually the afterpotential of the pacing pulse, which is in the order of hundreds of millivolts and lasts for tens of milliseconds after the end of a pacing pulse.³ It often encroaches into the...
native ER so that in order to reliably sense the ER, the polarization artifact has to be minimized or abolished.\textsuperscript{4} This feature labeled AutoCapture (Pacesetter Inc., St. Jude Medical Co., Sylmar, CA, USA) has been incorporated in the Microny\textsuperscript{®} and Regency\textsuperscript{®} (SC+ and SR+) models, of which the latter are available for clinical use in India. In a single-center study, its effectiveness was evaluated prospectively in conjunction with a low threshold, low polarization bipolar lead.

The objectives of this study were: (i) to evaluate the pacing threshold characteristics of the Membrane E leads over a 6-month follow-up utilizing the automatic capture threshold capability and diagnostics of Regency\textsuperscript{®} SC+ pulse generator; (ii) to assess the clinical performance of the AutoCapture\textsuperscript{™} algorithm as implemented in the ventricular demand (VVI) pacing systems with low polarization leads; and (iii) to study the safety and efficacy of the AutoCapture function.

**Methods**

The study included 54 patients (36 males, 18 females) undergoing permanent pacemaker implantation for symptomatic bradycardia due to a variety of causes including sick sinus syndrome (SSS) and high-grade atrioventricular block (Table 1). The mean age of the patients was 66 years. Clinical and 2-D transthoracic echocardiographic evaluation revealed an absence of structural heart disease in 25 patients (group I) while the other 29 patients had organic heart disease of multifactorial etiology (group II).

All patients received the VVI pacemaker Regency\textsuperscript{®} SC+2402L with the ventricular pacing lead Membrane E 1450T as recommended by the manufacturer (Pacemaker Inc.). In the majority of patients, the physician's judgment to use ventricular-based and fixed-rate pacing units depended on the economic affordability. All enrolled patients signed an informed consent prior to the implantation. The following data were collected from the patients' history and examination: age, gender, indications for pacing, type of arrhythmia, preimplant symptoms, concomitant cardiac conditions, and drug therapy at the time of implant.

**Pacemaker:** The VVI pacemaker Regency\textsuperscript{®} SC+ provides several automatic functions summarized by the AutoCapture\textsuperscript{™} algorithm.\textsuperscript{1} The idea of AutoCapture is to detect in a bipolar sensing configuration the presence of the ER signal between 15 and 62.5 ms after a unipolar pacing pulse. If the pacemaker detects no ER, a safety pacing pulse of 4.5 V amplitude and 0.49 ms duration is immediately delivered (Fig. 1). Besides the beat-to-beat safety control, the pacing pulse is automatically adjusted to the patient's pacing threshold. The threshold search is automatically activated after two consecutive losses of capture, resulting in the delivery of a back-up pulse, or every 8 hours, or with the application of a magnet. During a threshold search, the pacemaker reduces the pulse amplitude in steps of 0.3 V while holding the pulse duration constant until the pacing pulse becomes ineffective. The capture threshold is defined as the lowest amplitude that results in two consecutive captures. When two successive paced stimuli fail to capture, the pulse amplitude is automatically increased in 0.3 V steps until the capture is restored. When the threshold search is complete, the system automatically sets the output to 0.3 V above the capture threshold value. The device can monitor the evolution of stimulation threshold over time at different sampling intervals, ranging from 2 s to 24 hours. In the freeze mode, data collection stops when 256 samples have been acquired but these remain stored in the memory until retrieved by the physician at a follow-up visit. In the continuous mode, once 256 samples have been acquired, the system will delete the oldest data while storing the most recent measurements.

A potentially life-threatening condition may result if lead

**Table 1. Preimplant data and indications for pacing**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>66±13 (6–90)</td>
</tr>
<tr>
<td>Number of patients (males/females)</td>
<td>54 (38/16)</td>
</tr>
<tr>
<td>Side of the implant (left/right)</td>
<td>L30; R24</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>20.3±14.1</td>
</tr>
<tr>
<td>Structurally normal heart (2-D echocardiogram)</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>4</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>2</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
</tr>
<tr>
<td>Complete AV block</td>
<td>42</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>10</td>
</tr>
<tr>
<td>Sinus arrest</td>
<td>6</td>
</tr>
<tr>
<td>First-degree AV block</td>
<td>5</td>
</tr>
<tr>
<td>Tachy-brady syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>4</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>3</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>2</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
</tbody>
</table>

Each patient may have more than one indication

AV: atrioventricular
Implantation procedure and follow-up: All patients received a Regency® SC+ model 2402L (Pacesetter Inc.), a multiprogrammable, single-chamber, cardiac pulse generator with AutoCapture function programmed to VVI mode. The pacing system was implanted using standard endocardial implant techniques. Membrane E 1450 T leads with connector IS-1 BI (VS.12) were exclusively used in this study. A stringent implant protocol was followed and the pacing threshold, impedance, and spontaneous R-wave amplitude were measured using a standard pacing system analyzer (PSA). The pacing thresholds were determined at a pulse width of 0.42 ms, and stimulation impedance at an output of 5.0 V/0.42 ms. The minimum acceptable R-wave amplitude (bipolar intracardiac signal) was specified to 5 mV.

On the following day, measurements of standard pacing and sensing thresholds were obtained followed by the ER signal, ER sensitivity and polarization signal (PS) using the Pacesetter's Analyser Programmer System (APSµ) with the 3264.ENG software. Thereafter, the AutoCapture function was switched on in eligible patients. The minimum acceptable value for the ER signal was 4.0 mV. The measurements were repeated in all patients at 1 week (time of discharge from hospital) and at follow-up visits at 1, 3 and 6 months. Further evaluation in eligible patients was performed at 6-monthly intervals. At one-month follow-up, 24-hour Holter monitor studies were performed in selected patients (n = 25) who gave consent for the investigation. These Holters were automatically and manually analyzed for exits blocks, pauses, back-up pulses and pseudo (fusion) beats. When noncapture occurred, it was recorded whether or not there was an appropriate back-up pulse.

During the ER/PS assessment, the programmer turns the AutoCapture “off”, increases the pulse amplitude to 4.5 V for a series of paired pulses, and increases the pacing rate to 100 ppm. The first pulse in each pair captures the heart and produces an ER and PS. The second pulse, delivered 110 ms after the first, occurs when the myocardium is physiologically refractory, which allows for an independent measurement of lead polarization. In simpler terms, ER signal is the measure of the amplitude of myocardial depolarization resulting from the pacemaker stimulus while the PS is a measurement of the residual electrical charge from a pacing pulse. The pacemaker was programmed to AutoCapture ‘on’ with the sensitivity and ER setting as suggested by the programmer. The device determines an ER sense margin as close to 100% as possible, but minimally

Pacing lead: The Membrane E 1450 T is a tined, bipolar, steroid-eluting pacing lead with an electrode surface area of 3.5 mm². The electrode tip consists of titanium covered by titanium nitride. This is coated with a semipermeable membrane, which is also used as a steroid carrier (a copolymer with 13 µg of dexamethasone). The membrane and the titanium nitride tip are tissue tolerant, implying that only a minimum of fibrous tissue build-up occurs.

Fig. 1. Illustration of AutoCapture™ algorithm. (A) Detection window for evoked response and polarization signal. (B) Delivery of back-up safety pulse in the absence of ER detection. (C) Holter illustration of successful back-up pulse capture (arrows).
80%. To accomplish this, the amplitude of the signal resulting from the first pulse is divided by two. Of the available ER settings, the closest setting to this value is then compared to the PS. AutoCapture is not recommended if the amplitude of PS exceeds 60% of the proposed ER sensitivity. The pulse duration was set to 0.37 ms, and the stimulation threshold versus time counter was programmed in the 'freeze' mode at a sampling frequency of 1-hourly for 7 days, 6-hourly for 1 month, 12-hourly for 3 months, and 24-hourly every 6 months. The programmed and measured data along with the test results were obtained, recorded and printed at each evaluation session. All measurements for this study were performed at least twice in the supine position, and the mean of the two measurements is given. However, there were only minor differences between the two measurements.

**Statistical analysis:** The descriptive statistics in the report are expressed as mean±standard deviation (unless stated otherwise). The difference between the paired variables was calculated using appropriate t-tests. A p value of <0.05 was considered significant.

**Results**

The lead parameters at implantation are given in Table 2. In 19 patients, the R wave could not be assessed at the time of implant. At follow-up, the lead impedance and sensing parameters remained steady while the pacing thresholds increased significantly in the first week (0.5±0.17 V v. 0.78±0.39 V; p<0.001), with a further increase at one month (0.78±0.39 V v. 0.89±0.36 V; p<0.01) before stabilizing (Table 3). The results of the automatic capture function correlated well with the capture threshold measured using the Vario technique (Fig. 2).

![Fig. 2. Evolution of stimulation threshold during follow-up (AutoCapture™ v. Vario test).](image)

The ER signal remained stable with minimal variation (11.0±5.5 mV at implant, 10.7±4.9 mV at 6-month, and 11.1±4.7 mV at one-year follow-up). Two patients developed drug-induced renal failure and showed a steep decline in ER signal with concomitant rise in pacing thresholds in the first week, but surprisingly never regained the amplitude despite correction of uremia. One of them succumbed to pulmonary embolism during a prolonged pneumonic illness at 6 months, with the pacing thresholds once again rising progressively and the ER declining further prior to death (Fig. 3).

The PS showed a significant increase at 1 month (0.6±0.7 mV v. 1.0±0.6 mV; p<0.001) and stabilized thereafter (Fig. 4). The ER sensitivity throughout the follow-

---

**Table 2. Lead implantation parameters (n=54)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing threshold (V) at pulse width 0.42 ms</td>
<td>0.50±0.2</td>
</tr>
<tr>
<td>Lead impedance (ohm)</td>
<td>651.7±143.6</td>
</tr>
<tr>
<td>R wave (mV) (n=35)</td>
<td>12.1±5.4</td>
</tr>
</tbody>
</table>

**Table 3. Pacing and sensing parameters at follow-up**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1</th>
<th>Week 1</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (V) at PW 0.37 ms</td>
<td>0.50±0.17</td>
<td>0.78±0.39</td>
<td>0.89±0.36</td>
<td>0.89±0.37</td>
<td>0.87±0.41</td>
<td>0.90±0.46</td>
<td>0.81±0.25</td>
</tr>
<tr>
<td>Vario threshold (V) at PW 0.37 ms</td>
<td>0.49±0.19</td>
<td>0.73±0.34</td>
<td>0.85±0.35</td>
<td>0.84±0.36</td>
<td>0.85±0.40</td>
<td>0.87±0.40</td>
<td>0.78±0.26</td>
</tr>
<tr>
<td>Impedance (ohm) (n=54)</td>
<td>687±118</td>
<td>673±113</td>
<td>692±104</td>
<td>722±114</td>
<td>725±116</td>
<td>741±114</td>
<td>742±127</td>
</tr>
<tr>
<td>R-wave sensitivity (mV)</td>
<td>5.4±3.0</td>
<td>5.4±3.0</td>
<td>5.9±3.1</td>
<td>5.5±2.9</td>
<td>5.5±3.0</td>
<td>5.5±2.7</td>
<td>4.2±1.8</td>
</tr>
<tr>
<td>R-wave sensing margin (%)</td>
<td>159±42</td>
<td>157±34</td>
<td>161±41</td>
<td>159±45</td>
<td>160±36</td>
<td>165±41</td>
<td>163±37</td>
</tr>
<tr>
<td>ER signal (mV)</td>
<td>11.0±5.5</td>
<td>11.1±4.9</td>
<td>11.1±5.0</td>
<td>10.9±4.7</td>
<td>10.7±4.9</td>
<td>11.1±4.7</td>
<td>10.5±5.3</td>
</tr>
<tr>
<td>PS (mV)</td>
<td>0.6±0.7</td>
<td>0.8±0.7</td>
<td>1.0±0.6</td>
<td>1.1±0.5</td>
<td>1.1±0.5</td>
<td>1.2±0.4</td>
<td>1.2±0.5</td>
</tr>
</tbody>
</table>

PW: pulse width; ER: evoked response; PS: polarization signal

* v. p=NS; ** v. p<0.01
* v. ** and v. * p<0.001
up period varied between 3.8±1.5 and 5.6±2.3 mV (mean sensing margin 96%–156%). In three patients, the AutoCapture algorithm could not be switched on at day 1 because of low ER signal (ER 2.0–3.3 mV, n=2) and high PS (1.6 mV, n=1). The pacemaker recommended not to program the automatic threshold tracking ‘on’ in one patient permanently and in two patients intermittently. A fourth patient lost AutoCapture in the first week, which persisted into the first month (ER 3.1–3.3 mV, PS 1.0–1.1 mV), but subsequently regained the function as the PS stabilized at <1.0 mV despite a low ER (3.3–3.5 mV). Two patients had a low-to-borderline ER signal (3.3–4.6 mV) throughout the follow-up period but continued to show good AutoCapture function because of low PS (<1.0 mV). Hence the AutoCapture function could continue successfully even in patients with low ER signal provided PS remained low (<1.0 mV). At 6 months, the algorithm was consistently effective in 51 (94%) of 54 patients.

There was no difference in the ER signal according to gender and side of implant (Tables 4 and 5). However, in group II, the ER signal was significantly greater than that in group I (12.3±5.7 mV vs. 9.1±3.4 mV; p<0.05). Similarly, the ER sensitivity was numerically greater in group II both at the time of implant (4.2±1.6 mV vs. 3.4±1.2 mV; p<0.05) and at 6 months (6.5±2.8 mV vs. 4.7±1.1 mV; p<0.01). A comparison of the clinical and pacing parameters of the two study groups is given in Table 6.

In eligible patients with the AutoCapture ‘on’ the energy consumption was extremely low with the battery parameters remaining stable over time (Table 7, Fig. 5). Battery impedance can be used indirectly as an indicator for total current consumption over time. In all patients, the measured battery voltage remained constant at 2.78 V and

**Table 4. Evoked response (ER) signal (mV) in mean and women**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1</th>
<th>Week 1</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n=38)</td>
<td>10.8±5.5</td>
<td>11.3±4.6</td>
<td>11.2±4.8</td>
<td>11.1±4.7</td>
<td>10.9±5.1</td>
<td>10.1±4.3</td>
<td>10.3±5.3</td>
</tr>
<tr>
<td>Women (n=16)</td>
<td>11.7±5.6</td>
<td>10.5±5.5</td>
<td>10.7±5.7</td>
<td>10.2±4.6</td>
<td>10.5±4.7</td>
<td>12.9±5.2</td>
<td>15.6±3.0</td>
</tr>
<tr>
<td>N</td>
<td>54</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>38</td>
<td>18</td>
</tr>
</tbody>
</table>

p=NS for comparison at all times

**Table 5. Evoked response (ER) signal (mV) in left and right implants**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1</th>
<th>Week 1</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left (n=38)</td>
<td>11.9±6.3</td>
<td>11.0±4.9</td>
<td>11.3±5.1</td>
<td>11.3±4.7</td>
<td>11.0±5.1</td>
<td>10.9±3.9</td>
<td>12.5±5.6</td>
</tr>
<tr>
<td>Right (n=16)</td>
<td>9.9±4.1</td>
<td>11.1±4.9</td>
<td>10.9±5.0</td>
<td>10.3±4.6</td>
<td>10.4±4.9</td>
<td>10.9±5.1</td>
<td>10.7±5.4</td>
</tr>
<tr>
<td>N</td>
<td>54</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>38</td>
<td>18</td>
</tr>
</tbody>
</table>

p=NS for comparison at all times
the impedance was in the preimplant range (<1000 ohm) at the last recorded follow-up visit. The term 2×T is used to denote a state had the AutoCapture function not been switched on and the pulse amplitude of the pacemaker been manually programmed to twice the pacing threshold as is the conventional practice. Autobatch refers to a set of automatically programmed values that the pacemaker reverts to if the AutoCapture function is sporadically turned off. Factory settings yield those values where the pacemaker has never been programmed after implantation, a relatively rare condition in patients who follow-up regularly at tertiary care hospitals having pacemaker clinics. A similar statistical trend emerged in the pacing parameters in all modes in groups I and II. There was no significant difference in the parameters between the groups (Table 8).

Twenty-four Holter monitor recordings were obtained in 25 patients (Table 9). In a total recorded time of 580 hours, there were 200 episodes (0.4% of all paced events) of loss of capture by initial impulse, either spontaneous or during threshold checks, all of which were backed up by a high voltage output (Fig. 1C). In 7 patients (28%), there were 24 episodes of back-up pulse delivery during native or fusion beats (0.25%) of all paced events (Fig. 6). There was no incidence where delivery of back-up pulses occurred despite capture of the initial impulse, as indicative of ER undersensing. The likelihood of multiple occurrences of pseudofusion beats had a correlation with the presence of spontaneous cardiac activity.

### Table 6. Clinical and pacing parameters in group I and group II

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n=25)</th>
<th>Group II (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.1±6.5</td>
<td>67.8±9.4</td>
</tr>
<tr>
<td>Gender</td>
<td>M: 17; F: 8</td>
<td>M: 21; F: 8</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AVB: 19; SSS: 6</td>
<td>AVB: 23; SSS: 6</td>
</tr>
<tr>
<td>Sidedness (left/right)</td>
<td>L: 12; R: 13</td>
<td>L: 18; R: 11</td>
</tr>
<tr>
<td>Implant pacing threshold (V)</td>
<td>0.46±0.19</td>
<td>0.48±0.20</td>
</tr>
<tr>
<td>Implant impedance (ohm)</td>
<td>650±105.3</td>
<td>653.3±140.2</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>21.8±15.4</td>
<td>19.0±13.2</td>
</tr>
<tr>
<td>Pacing threshold (V) at 6 months</td>
<td>0.90±0.49</td>
<td>0.84±0.33</td>
</tr>
<tr>
<td>Pulse amplitude (V) at 6 months</td>
<td>1.22±0.49</td>
<td>1.15±0.33</td>
</tr>
<tr>
<td>Pulse current (mA) at 6 months</td>
<td>1.62±0.63</td>
<td>1.72±0.71</td>
</tr>
<tr>
<td>Pulse charge (µC) at 6 months</td>
<td>0.66±0.43</td>
<td>0.61±0.28</td>
</tr>
<tr>
<td>Pulse energy (µJ) at 6 months</td>
<td>0.85±0.73</td>
<td>0.78±0.58</td>
</tr>
<tr>
<td>Battery current (µA) at 6 months</td>
<td>3.21±0.44</td>
<td>3.17±0.31</td>
</tr>
<tr>
<td>ER signal (mV) at 6 months</td>
<td>9.1±3.4*</td>
<td>12.3±5.7*</td>
</tr>
<tr>
<td>PS (mV) at 6 months</td>
<td>1.2±0.4</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td>R sensitivity (mV) at last follow-up</td>
<td>4.90±3.4</td>
<td>6.1±2.9</td>
</tr>
<tr>
<td>(mean sensing margin)</td>
<td>(162%)</td>
<td>(165%)</td>
</tr>
<tr>
<td>ER sensitivity (mV) at last follow-up</td>
<td>3.4±1.2</td>
<td>4.7±1.1**</td>
</tr>
<tr>
<td>(mean sensing margin)</td>
<td>(96%)</td>
<td>(150%)</td>
</tr>
</tbody>
</table>

AVB: atioventricular block; SSS: sick sinus syndrome
*p<0.05; **p<0.01

### Table 7. Energy parameters in AutoCapture on patients (n=51) at 6-month follow-up

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AutoCapture (6 months)</th>
<th>2×T</th>
<th>Autobatch</th>
<th>Factory setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse amplitude (V)</td>
<td>1.19±0.42</td>
<td>1.91±0.89</td>
<td>2.82±0.71</td>
<td>3.98±0.16</td>
</tr>
<tr>
<td>Pulse current (mA)</td>
<td>1.68±0.66</td>
<td>2.75±1.16</td>
<td>4.0±1.18</td>
<td>5.8±1.28</td>
</tr>
<tr>
<td>Pulse charge (µC)</td>
<td>0.63±0.36</td>
<td>0.93±0.40</td>
<td>1.40±0.46</td>
<td>2.03±0.43</td>
</tr>
<tr>
<td>Pulse energy (µJ)</td>
<td>0.82±0.66</td>
<td>2.10±0.26</td>
<td>4.05±2.51</td>
<td>7.68±1.46</td>
</tr>
<tr>
<td>Battery current (µA)</td>
<td>3.18±0.37</td>
<td>3.82±1.22</td>
<td>5.0±2.51</td>
<td>7.65±1.62</td>
</tr>
</tbody>
</table>

*p=0.01 for AutoCapture v. 2×T; for all other parameters, p<0.001

### Table 8. Energy parameters in group I and group II patients at 6-month follow-up

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AutoCapture (6 months)</th>
<th>2×T</th>
<th>Autobatch</th>
<th>Factory setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse amplitude (V)</td>
<td>1.22±0.49</td>
<td>1.15±0.33</td>
<td>1.94±1.01</td>
<td>1.86±0.71</td>
</tr>
<tr>
<td>Pulse current (mA)</td>
<td>1.62±0.63</td>
<td>1.72±0.71</td>
<td>2.66±1.22</td>
<td>2.83±1.12</td>
</tr>
<tr>
<td>Pulse charge (µC)</td>
<td>0.66±0.43</td>
<td>0.61±0.28</td>
<td>0.89±0.38</td>
<td>0.96±0.41</td>
</tr>
<tr>
<td>Pulse energy (µJ)</td>
<td>0.85±0.73</td>
<td>0.78±0.58</td>
<td>2.43±2.81</td>
<td>1.90±1.58</td>
</tr>
<tr>
<td>Battery current (µA)</td>
<td>3.21±0.44</td>
<td>3.17±0.31</td>
<td>3.97±1.55</td>
<td>3.69±0.84</td>
</tr>
</tbody>
</table>

*p=0.01 for AutoCapture v. 2×T; for all other parameters in groups I and II, p<0.001

p=NS for 2×T v. Autobatch; for all other parameters in groups I and II, p<0.001
At 6 months, an elderly female patient inflicted with a pneumonic illness succumbed to pulmonary embolism (Fig. 3). In another patient, a microdisplacement of the lead was suspected since a persistently high voltage stimulation was observed despite normal pacing parameters during the entire follow-up (Fig. 7). The other adverse events are summarized in Table 10.

Table 9. Holter monitoring data (n=25)

<table>
<thead>
<tr>
<th>Events</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total record time</td>
<td>580 hours</td>
</tr>
<tr>
<td>Total QRS complexes recorded</td>
<td>2 520 000</td>
</tr>
<tr>
<td>Total paced QRS complexes*</td>
<td>2 088 000 (83% of total QRS)</td>
</tr>
<tr>
<td>Loss of capture (200 episodes)</td>
<td>8352 (0.4% of paced QRS)</td>
</tr>
<tr>
<td>R-wave undersensing (n=7, 24 episodes)</td>
<td>5200 (0.25% of paced QRS)</td>
</tr>
<tr>
<td>ER undersensing</td>
<td>Not recorded</td>
</tr>
</tbody>
</table>

*Excludes fusion, pseudofusion and native beats

Table 10. Summary of adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (fatal pulmonary embolism)</td>
<td>1</td>
</tr>
<tr>
<td>Embolic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>1</td>
</tr>
<tr>
<td>Pacemaker syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Pacemaker not needed</td>
<td>1</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 5. Energy consumption in AutoCapture-eligible patients. (A) Pulse parameters. (B) Battery parameters.

Fig. 6. (A) Intermittent high-voltage stimulation secondary to R-wave undersensing. (B) Holter illustration of ventricular undersensing (arrows).

Fig. 7. Lead microdisplacement: persistent high-voltage stimulation in a patient with normal AutoCapture™ parameters.
Discussion

The concept of a threshold tracking pacemaker was proposed by Preston and Bowers almost three decades ago.\(^5\) Ever since, various investigators have studied the depolarization signal emanating from ventricular capture and tried to differentiate it from the polarization artifact.\(^2,3,4,6\) The first reported clinical experience with AutoCapture was an Italian multicenter study (PACEMATE Study Group) which evaluated 54 patients implanted with the Microny\(^6\) SR+2425T SSIR pacemaker at 19 centers.\(^7\) The bipolar Membrane leads used in this study were either impregnated or not with steroid. With both these leads, the evolution of pacing thresholds was identical over a 6-week period.

The European Microny Study Group systematically followed up 113 patients from 16 centers for 1 year.\(^1\) All patients underwent a 24-hour Holter recording at 1-month follow-up that confirmed total reliability of this algorithm without any exit block. The acute and chronic thresholds measured by Vario and AutoCapture tests correlated over the study period, and the measured ER signal also remained stable over time.

The present study confirms the reliability and effectiveness of the combination of Membrane leads and Regency\(^6\) SC+ pulse generators. Over a mean follow-up of 20 months, stable and adequate sensing and ER thresholds were found along with low capture thresholds, and the ability to automatically program a low output, maximizing the system longevity without compromising patient safety. At 6 months, the algorithm was consistently effective in 51 of 54 patients. It is well known that myocardial capture and sensing thresholds evolve over time and may be affected by several factors.\(^8,9\) It is also clear that there is no correlation between acute and chronic stimulation thresholds, due to various factors that are involved in the maturation of the tissue–electrode interface.\(^10\) The increase in stimulation threshold during the first several weeks is related to the development of a conductive but nonexcitable fibrotic capsule that encases the tip of the electrode. After 3–4 weeks, the inflammation subsides and the threshold may subsequently decline, remain stable, or increase depending on the chronic foreign body response at the electrode–tissue interface.\(^11\)

In this study there was a statistically significant difference between the threshold at implant and week 1 \((p<0.001)\) with a further significant rise at month 1 \((p<0.01)\) after which there were no significant threshold modifications. The mean Vario threshold was marginally lower than the AutoCapture threshold which is consistent with the pacemaker design, i.e. capacitor's output is 0.1 V higher than the marked value during the Vario test.\(^12\) A margin of 1.5–2 times with respect to the voltage threshold is recommended to safeguard against the expected but unpredictable waxing and waning thresholds to minimize the risk of exit block.\(^13\) This happens to be the standard practice in pacemaker programming, but it produces excessive battery current drain and rarely may result in loss of capture if the threshold exceeds the programmed output. The AutoCapture values of pulse and battery parameters were much lower than the 2×T and Autobatch values (Tables 7 and 8) \((p<0.01–0.001)\) which translated into lower pulse energies required to pace the heart along with lower battery current drain. This predicts extended longevity of the device. However, the current consumption for stimulation was measured at each visit; and the percentage of pacing and back-up ratio were not taken into account. Therefore, the current consumption for stimulation may vary between patients and the internal current drain should also be added when estimating the total current consumption. The battery impedance can also be used as an indirect parameter of total current consumption over time. All our patients had the battery impedance in the preimplant range \((<1000 \text{ ohm})\) at their last follow-up visit.

R-wave sensing remained stable in the patients over time, there being no significant difference between or within the groups. Similarly, the ER signal remained steady on follow-up, but it was significantly greater in group II as was the numerical value of ER sensitivity. Since group II comprised patients with hypertrophied ventricles (on 2-D echocardiography), it is possible that the amplitude of ER signal is related to the muscle mass. Interestingly, the ER declined steeply in the first week in two patients who developed drug-induced renal failure and never really recovered despite reversal of the uremic state. Similarly, the ER showed a further progressive decline in one of these patients who developed a prolonged pneumonic illness and succumbed to pulmonary embolism at 6 months. These events possibly indicate the adverse effects of uremia and pulmonary hypertension on right ventricular myocardial depolarization. While the AutoCapture algorithm could not be switched ‘on’ in 3 patients at day 1 because of low ER signal and high PS, there were an equal number of patients who had low ER but also low PS which allowed the algorithm to function successfully. This is in agreement with the concept that the main reason not to activate AutoCapture in these patients is primarily the increase in PS and not the decrease in ER amplitude.\(^14,15\) In a recent study involving 398 patients from 42 centers, the ER exhibited a small increase over a mean period of 1 year.\(^16\)
However, that did not result in an improvement of the AutoCapture function in patients with inadequate values at implant. Approximately 10% of patients could not have AutoCapture enabled due to suboptimal ER/PS signal despite satisfactory R wave and pacing thresholds. Unfortunately, patients with low ER signal cannot be identified in advance by their electrical and clinical data, since at present, it cannot be determined by any PSA and there is no known parameter that can help optimize the amplitude. As the ER derives from unipolar ventricular pacing, we assumed that the parameters that relate to the pacing pulse could be beneficial. However, right- and left-sided pacing pulses did not influence the ER amplitude and the pacing threshold, and the pacing impedance did not correlate with the ER signal. Also, the ER was not affected by gender. These observations are in agreement with a recent study.17

Our Holter assessment of the 25 select patients was a laborious exercise, since the Holter system lacked the software for advanced pacemaker analysis, and the analysis was carried out manually by two different investigators. The total number of paced QRS complexes formed more than 80% of the total QRS complexes. All episodes of loss of capture were followed by high voltage stimulation (Fig. 1C), and ventricular undersensing was seen in 28% of the patients which constituted 0.25% of all paced beats (Fig. 6B). This study did not find any Holter evidence of ER undersensing. It has been shown in earlier studies that more than 20% of pseudofusion beats induce back-up pulses and these pseudofusion beats account for the majority (>85%) of all back-up pulses.1

In a randomized study with Regency® SC+ and SR+ pacemakers, 162 patients were followed up at 27 Spanish centers for 6 months. About 10% of the patients with the algorithm showed high voltage stimulation, half of whom showed a high number of fusion and pseudofusion beats.18 Similarly, in the North American multicenter study, the Holter assessment in 51 consecutive patients revealed high voltage back-up pacing in the event of an exit block in all. The exit block constituted 0.4% of all paced events. The incidence of R wave and ER undersensing was 0.3% and 0.001% of all paced events, respectively.16 The other causes of high voltage stimulation include poor ER signal, high capture threshold and microdisplacement of lead, which were also observed in this study.

We report our experience with the AutoCapture™ algorithm in the Regency® SC+ pulse generator, that provided automatic confirmation of ventricular capture, adjustment of output and continuous threshold monitoring. It functioned in providing safe low-output pacing in the majority (>90%) of patients during a limited follow-up period. The algorithm decreased the battery drain compared to the AutoCapture ‘off’ settings, thereby prolonging the service life of the generator. The high energy back-up pulse during exit block provided an additional safety feature over conventional devices. However, this algorithm could not distinguish pseudofusion beats from the genuine loss of capture while delivering back-up pulses. The ER signal remained stable throughout the study period, while the PS increased significantly in the first month and remained steady subsequently. Importantly, even though PSAs that measure ER signal are yet to become available, a standard implantation technique with the recommended lead provided an acceptable rate of maintenance of the AutoCapture function. To the best of our knowledge, this is the largest single center experience being reported.

References
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15. Lau C, Nishimura SC, Philippon F. Polarization signal and evoked
response characteristics in current endocardial electrodes [Abstr].


Atrioventricular (AV) synchronous pacing, with or without rate adaptivity, is currently favored in cases with symptomatic AV nodal (AVN) disease. This mode of pacing offers several advantages: (i) it improves cardiac output; (ii) decreases the chances of development of pacemaker syndrome; and (iii) prevents atrial fibrillation and other atrial tachyarrhythmias. This last effect protects against systemic embolization and thus prolongs life expectancy as well as improves the quality of life.1–6 Though the cost of implantation is considerable, the long-term therapeutic costs may be reduced by AV synchronous pacing.7

Atrioventricular synchronous pacing can be done by either a dual-lead DDD/DDDR or by single-lead VDD/DDD (in patients with sick sinus syndrome) mode. Double-lead systems have many disadvantages—implantation is technically difficult as dual venous access is required; the cost is high because two leads are used; and atrial lead dislodgment and wastage are frequent. Atrial lead wastage occurs due to fracture of the wire retaining the J-shape of the lead. Single-lead pacing, therefore, has gained popularity.8

Atrial pacing by a single-lead DDD pacing using the conventional pulses, however, results in a high pacing threshold, and can lead to diaphragmatic contraction due to phrenic nerve stimulation in a significant number of cases. To tackle this problem, two atrial rings are currently used in the single lead. The proximal ring emits a positive polarity wave and, simultaneously, the distal ring emits a negative polarity wave of the same amplitude and width—these two waves overlap each other. These two separate impulses stimulate the atrial myocardium concurrently, thereby decreasing the pacing threshold. This technique is called overlapping biphasic impulse (OLBI) stimulation.9

The current prospective study was undertaken to evaluate the long-term performance of single-pass pacing using the overlapping biphasic impulse stimulation technique.

**Background:** Single-pass physiological pacing has several advantages over dual-lead physiological pacing. The present study evaluated the long-term performance of single-pass pacing using the overlapping biphasic impulse stimulation technique.

**Methods and Results:** A total of 30 patients with single-pass VDD pacing and 8 patients with single-pass DDDC pacing were followed up for 1 year by basal and magnet electrocardiograms and real-time telemetry. All the patients showed satisfactory atrial sensing and pacing capture threshold. The atrial sensing thresholds at implant and at 1 month, 3 months, 6 months and 12 months of follow-up were 2.5±0.67 mV, 1.6±0.6 mV, 1.1±0.5 mV, 1.0±0.5 mV and 1.0±0.04 mV, respectively. The corresponding values for atrial pacing threshold at a pulse wave of 0.3 ms were 2.5±1.0 V, 4.4±0.9 V, 3.8±1.2 V, 3.6±1.4 V and 3.8±1.4 V. Of the patients with DDDC pacing, 88% showed stable pacing capture in the supine position, 75% in the upright position and 62% in both positions. Diaphragmatic contraction was seen in 25% of cases with DDDC pacing. No such event was seen in patients with VDD pacing.

**Conclusions:** Single-pass pacing is safe, technically easy and cheap as compared to dual-lead systems. However, it would be prudent to recommend DDDC pacing in patients who require predominantly VDD pacing and only occasionally atrial pacing, as the latter showed a low percentage of stable atrial pacing capture in both upright and supine positions as well as a significant percentage of diaphragmatic contraction. (Indian Heart J 2001; 53:477–480)

**Key Words:** Pacemaker, Physiological pacing, Heart block
assess the long-term results of OLB single-lead AV synchronous pacing and single-lead VDD pacing.

Methods

A total of 145 patients (age range 26–70 years) with complete or intermittent AV block, who attended the outpatient or emergency department of the cardiology unit of SSKM Hospital between January 1997 and December 2000, were enrolled for the study. All the patients underwent 24-hour Holter monitoring and exercise testing to detect any chronotropic incompetence. The exclusion criteria were: (i) chronotropic incompetence (i.e. achieving <100 beats/min with exercise); and (ii) persistent atrial fibrillation. After the screening tests, 50 patients were excluded from the study as they could not fulfill the inclusion criteria and received VVI/VVIR pacing systems. Another 57 patients also received VVI/VVIR pacing systems as they could not afford the cost of the single-pass system and were excluded from the study. Of the remaining 38 patients (30 males and 8 females) finally included in the study, 30 patients had no evidence of sinus node disease and were taken up for VDD pacing with a single lead. The remaining 8 patients had sinus node disease and therefore underwent DDD pacing with an OLB single lead (DDDC mode). The pacemaker systems used were—(A) for VDD: (i) Prodigy 8168 (Medtronic) (n=12), (ii) Dromos (Biotronik) (n=4), and (iii) Advent 2060 LR (Pacesetter) (n=14); and (B) for DDDC: Eikos SLW (Biotronik) (n=8).

The single-pass lead was introduced through the right cephalic vein in 29 patients. This procedure failed in the remaining 9 patients and the lead was introduced through the right subclavian vein using a percutaneous lead introducer. The distal end of the single-pass lead was positioned at the right ventricular apex so as to achieve a pacing threshold of less than 1 V and an R wave of more than 5 mV. The floating atrial rings were then positioned at either high- or mid-right atrium, with an adequate loop so that the "p" wave amplitude was more than 0.5 mV during both inspiration and expiration. The position with the lowest capture threshold and highest "p" wave sensing was selected. The lead was then fixed by a ligature on the sleeve and sutured. It was connected with the corresponding pacemaker (VDD or DDDC) and placed in the subcutaneous pocket. After implantation, all the patients were monitored for 24 hours to detect any sensing or pacing failure. They were discharged after removal of stitches on postoperative day 7 and advised follow-up at the pacemaker clinic.

Follow-up: Each patient was followed up at 1 month, 3 months, 6 months and 12 months after pacemaker implantation with basal and magnet electrocardiograms (ECGs) taken at each visit. In every patient, the following data were actively recruited by real-time telemetry: (i) ventricular sensing and pacing threshold; (ii) atrial sensing threshold; and (iii) atrial pacing threshold (only in patients with DDDC pacing). These observations were taken in both the supine and sitting positions.

Statistical analysis: All the values were expressed as mean±SD. A p value <0.05 was taken as significant when the follow-up data were compared with the acute implant data.

Results

All 38 patients were followed up postprocedure for 12 months. The mean (±SD) values of the acute implant threshold and real-time telemetry data at each follow-up are presented in Tables 1 and 2.

### Table 1. Acute pacemaker implant thresholds

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Implant 1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Ventricular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R wave</td>
<td>11.03±2.22 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capture threshold</td>
<td>0.63±0.13 V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1.06±0.37 mA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Atrial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;p&quot; wave amplitude</td>
<td>2.5±1.3 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial capture</td>
<td>2.61±1.1 V</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Real-time telemetry data on follow-up

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Implant 1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial sensing</td>
<td>2.5±0.67 mV</td>
<td>1.6±0.6*</td>
<td>1.1±0.5*</td>
<td>1.0±0.5*</td>
</tr>
<tr>
<td>Atrial pacing</td>
<td>2.5±1.0 V</td>
<td>4.4±0.9*</td>
<td>3.8±1.2</td>
<td>3.6±1.4</td>
</tr>
<tr>
<td>PW (0.5 ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular</td>
<td>8.0±2.3 mV</td>
<td>8.0±2.4</td>
<td>7.8±2.3</td>
<td>7.9±2.1</td>
</tr>
<tr>
<td>Ventricular</td>
<td>0.8±0.34 mV</td>
<td>2.4±0.40</td>
<td>1.2±0.32</td>
<td>1.3±0.32</td>
</tr>
<tr>
<td>PW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PW: pulse width  
*p<0.05

During follow-up, the atrial sensing threshold showed a significant drop at 1 month, and thereafter stabilized at a significantly lower value throughout the rest of the follow-up period.
The atrial pacing capture threshold rose significantly above the acute threshold at 1 month, but thereafter stabilized at a lower value from 3 months onwards. However, this lowering of the pacing threshold value was not significant when compared with the acute implant data (Table 2). In 7 out of 8 patients (88%) with DDDC pacing, at least 80% of the atrial spikes induced a “p” wave in the follow-up ECGs, thereby satisfying the North American Society of Pacing and Electrophysiology (NASPE) criteria of stable pacing capture of the atrium. In 2 out of 8 patients (25%) with DDDC pacing, diaphragmatic contraction was noted with atrial spikes. No such event was seen in patients with single-pass VDD pacing.

The effect of atrial capture in the supine and upright positions in patients with DDDC pacing is presented in Fig. 1. Seven out of 8 patients (88%) were responsive to atrial pacing in the supine position throughout the 1-year follow-up period. Five out of 8 patients (62%) were responsive to atrial pacing in the supine position in the immediate postimplant stage and at 3 months, but from 6 months onwards, 6 patients (75%) became responsive to atrial pacing in this position. Five out of 8 patients (62%) were responsive to atrial pacing in both the supine and upright positions throughout the 1-year follow-up period.

Adequate ventricular pacing was seen in all patients in both the VDD and DDDC modes (Table 1).

The conventional single-pass lead results in a high pacing threshold and significant diaphragmatic contraction. This problem is circumvented by using the OLBI principle. In the present study, though the acute atrial pacing threshold was high in the DDDC mode, the chronic pacing threshold was low. A dequate ventricular tracking of the atrial rate was achieved in all cases on the threshold values were established. However, diaphragmatic contraction was noted in 25% of cases in the DDDC mode. No such event was noted in patients with single-pass VDD pacing.

As the OLBI principle involves the use of floating atrial electrodes, achieving stable atrial pacing in different positions is of primary concern during long-term follow-up. In the present study, 80% of the patients showed stable atrial pacing in the supine position and 75% in the upright position but only 62% showed stable atrial pacing in both the supine and upright positions. Similar observations were reported by Bongiorni et al. A further drawback of using atrial dipoles in OLBI is that they may sense far-field cardiac events like R wave and skeletal myopotentials or afterpotentials. These far-field sensings obviously reduce AV synchrony. The problem is usually tackled by adjustment of the refractory periods. In the present study, no such oversensing problem was noted.

Longo et al. reported two cases with pacemaker-mediated tachycardia associated with retrograde conduction in their follow-up of 36 patients with single-pass VDD pacing system. In the present study, no such complication was noted.

Conclusions: We conclude that single-pass VDD and DDDC pacing using the OLBI principle are safe and technically easy and do not have the problem of atrial lead dislodgment or fracture. They are also economically cheaper than the conventional dual-lead DDD mode. A chronic atrial sensing was satisfactory in our study, atrial tracking in both VDD and DDDC modes was adequate. However, since chronic stable atrial pacing was seen in only 62% of patients in all positions and 25% of cases had diaphragmatic contraction, single-pass DDDC pacing with floating atrial rings using the OLBI principle should be used in patients who require predominantly VDD pacing and only occasionally atrial pacing. Thus, the single-pass lead system with floating atrial rings requires further refinement to ensure better long-term outcome for atrial pacing.

**References**

1. Lames GA, Orav EJ, Stambler BS, Ellenbogen KA, Sgarbossa EB, Huang SK, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-
Pheochromocytoma: A 10-Year Experience in a Tertiary Care North Indian Hospital

N Sharma, S Kumari, S Jain, S Varma
Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh

Background: The study was carried out to highlight the clinical and biochemical profile of patients with pheochromocytoma in a tertiary care center of North India.

Methods and Results: Thirty consecutive cases of pheochromocytoma admitted over a period of 10 years to our Institute were analyzed. The chief clinical complaints of these 30 patients (17 males and 13 females, mean age 24 ± 7 years) were palpitation (80%), headache (77%), sweating (60%), breathlessness (67%) and flushing (56%). The clinical triad of headache, flushing and sweating occurred in 26.7% of cases. On clinical examination, 97% of the patients were hypertensive and 16.6% presented with malignant hypertension. Laboratory measurements showed that the levels of 24-hour urinary vanillylmandelic acid were elevated in 80% of cases. Levels of plasma adrenaline and noradrenaline were raised in 78% and 79% of cases, respectively. Anatomical localization of the tumor on computerized tomographic scan showed the presence of an adrenal tumor in 80% and extra-adrenal tumor in 20%. Surgical removal of the tumor could be carried out in 28 cases following control of the blood pressure with antihypertensive drugs including alpha and beta adrenoreceptor blockers.

Conclusions: Pheochromocytoma should be suspected in all young hypertensive persons. The appropriate therapy for this tumor is surgical removal preceded by adequate blood pressure control including the use of alpha and beta adrenoreceptor antagonists. (Indian Heart J 2001; 53:481-485)

Key Words: Pheochromocytoma, Hypertension, Tumor

Secondary hypertension accounts for 5%-8% of all cases of hypertension. Among the different causes of secondary hypertension, pheochromocytoma is responsible for 0.05%-0.3%. A careful diagnosis of the tumor requires a high index of suspicion coupled with laboratory demonstration of excess catecholamine secretion. The present study was carried out in a tertiary care hospital of north India to study the profile of patients with pheochromocytoma.

Methods

From January 1989 to December 1996, data of patients with pheochromocytoma were obtained from the records of patients attending the hypertension clinic of the Nehru Hospital which is attached to the Post Graduate Institute of Medical Education and Research, Chandigarh, India. From January 1997 onwards, patients were studied prospectively.
contrast enhanced computerized tomographic (CT) scan of the chest and abdomen were carried out.

**Results**

Of the 30 patients with pheochromocytoma, there were 17 males and 13 females. The main complaints of our patients are given in Table 1. The clinical triad of headache, flushing and sweating was present in only 8 (26.7%) cases. A history of hypertension of either persistent or intermittent nature could be elicited in 29 cases. In one case, the tumor was accidentally discovered during ultrasonographic screening for gall stones. In this patient, there were neither any clinical features nor any abnormalities in laboratory estimations of catecholamines to suggest the diagnosis of pheochromocytoma.

The blood pressure data of our patients are presented in Table 2. A hypertensive crisis (malignant hypertension) was seen in 5 cases (16.6%). Of the 30 cases, 6 did not have the clinical features, clinical triad, paroxysmal hypertension or a postural fall of the systolic blood pressure typical of pheochromocytoma. Changes characteristic of grade I hypertensive retinopathy were seen in 2 cases (6.6%), grade II in 19 (63.3%), grade III in 2 (6.6%) and grade IV in 5 (16.6%). One patient showed evidence of metastatic pheochromocytoma on fine needle aspiration cytology for inguinal lymphadenopathy. Associated findings present were hypertrophic cardiomyopathy in 1, annulo-aortic ectasia with aortic regurgitation in 1, neurofibromatosis type 1 in 2 and gall stones in 1.

Specific laboratory investigations for pheochromocytoma revealed that the 24-hour urinary excretion of VMA was normal in 20% (normal 8 mg/total urinary volume) but it was elevated 1–1.5 times the normal limit in 20%, 1.5–2.0 times in 16.7% and more than double the normal limit in 43.3% of cases. Estimation of 24-hour urinary adrenaline excretion within the normal limit (normal 24 µg/24 hours). In 7, it was raised 1–1.5 times the normal limit and in 1 case each was elevated 1.5–2 times and more than double the normal limit, respectively. In 16 cases, the 24-hour urinary noradrenaline excretion was measured and was within 1–1.5 times the normal limit (normal 66 µg/24 hours) in all. In 6 cases where the urinary VMA excretion was within the normal limit, urinary estimation of noradrenaline was not carried out. Five of these 6 cases had clinical features suggestive of pheochromocytoma. In 23 patients, blood samples were taken for estimating the plasma adrenaline and noradrenaline levels. Plasma adrenaline was elevated 1–1.5 times, 1.5–2 times and more than double the normal limit in 13, 1 and 4 cases, respectively (normal 0.4 ng/ml), respectively. Tumor localization carried out by CT scanning disclosed an adrenal tumor in 80% and an extra-adrenal tumor in 20% of cases (1 near the right renal hilum, 1 in the bladder wall and 4 arising from the Organ of Zuckerkandl). In the single pregnant patient, an ultrasonic examination of the abdomen showed a nonviable growth-retarded fetus. After control of the blood pressure with drugs, she underwent a medical termination of pregnancy followed by surgical extirpation of the tumor. There were 2 cases of malignant pheochromocytoma with a palpable abdominal mass. In 1, the confirmation of malignancy was made on fine needle aspiration cytology of the inguinal

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>24±7 years</td>
</tr>
<tr>
<td>Palpitation</td>
<td>80%</td>
</tr>
<tr>
<td>Headache</td>
<td>77%</td>
</tr>
<tr>
<td>Flushing</td>
<td>56%</td>
</tr>
<tr>
<td>Sweating</td>
<td>60%</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>67%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (6.6)</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Tumor localization (on computerized tomography)</td>
<td></td>
</tr>
<tr>
<td>Adrenal</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Right</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Extra-adrenal</td>
<td>6 (20)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>SBP (mmHg)</th>
<th>n</th>
<th>DBP (mmHg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>140–159:</td>
<td>3 (10)</td>
<td>90–99:</td>
<td>2 (66)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160–179:</td>
<td>1 (3.3)</td>
<td>100–109:</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>≥180:</td>
<td>25 (83.3)</td>
<td>≥110:</td>
<td>21 (70)</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure

Value in parentheses are percentages
Pheochromocytomas are tumors of neuroectodermal origin, presenting clinically with the triad of headache, diaphoresis and palpitation. This clinical triad is suggestive of pheochromocytoma and peculiar to the specific patient population but occurs in only 11%–22% of cases.7–13 In our study, it was seen in 26.7% of patients. Hypertension of a persistent or paroxysmal nature is one of the leading clues for the diagnosis of pheochromocytoma. Twenty-nine out of the 30 cases in our study were hypertensive and in 7%, i.e. 2 cases of malignant pheochromocytoma, three antihypertensive agents (amlodipine, prazocin and atenolol) were used in maximum tolerated doses.

**Discussion**

Pheochromocytomas are tumors of neuroectodermal origin, presenting clinically with the triad of headache, diaphoresis and palpitation. This clinical triad is suggestive of pheochromocytoma and peculiar to the specific patient population but occurs in only 11%–22% of cases.7–13 In our study, it was seen in 26.7% of patients. Hypertension of a persistent or paroxysmal nature is one of the leading clues for the diagnosis of pheochromocytoma. Twenty-nine out of the 30 cases in our study were hypertensive and one was normotensive. A review of the National Cancer Registry in Sweden showed that of 439 cases of pheochromocytoma, nearly 40% were diagnosed at autopsy and, of these, the findings were reported as incidental in 14%.14 In another review from the Mayo Clinic of 54 cases of pheochromocytoma, Loh et al.7 measured urinary VMA excretion in 6 cases; all 6 had an elevated level of plasma or urinary catecholamines. Modlin et al.9 in a study of 72 cases of pheochromocytoma showed elevated levels of urinary catecholamines in 93%. In our study, levels of plasma noradrenaline and adrenaline were measured in 23 out of 30 cases. The levels of plasma noradrenaline were raised in 78.7% and of adrenaline in 78.3% of cases. Other studies have shown that in 90%–95% of patients with this tumor, levels of plasma adrenaline and noradrenaline are markedly elevated; the sensitivity and specificity of this test is 85% and 95%, respectively.7,9,18
localize an abdominal tumor greater than 1 cm in size.\textsuperscript{19,20}
For adrenal masses of less than 1 cm and for extra-adrenal masses, this accuracy decreases. However, CT scanning cannot differentiate between pheochromocytoma, adenoma and metastasis.\textsuperscript{18-20} In our study, CT could localize abnormal pheochromocytoma in all the cases (sensitivity of 100%). There were 6 tumors (20%) located extra-adrenally. Extra-adrenal pheochromocytomas account for approximately 11\%–27\%.\textsuperscript{9,12,13} of all pheochromocytomas and less than 1\% of these arise in the bladder wall from the sympathetic nervous system.\textsuperscript{21} Bladder tumors are usually localized to the trigone and such patients give a characteristic history of adrenergic symptoms on micturition, which was the case in our patient.

Occurrence of pheochromocytoma in pregnancy ushers in considerable risk to both the mother and fetus. A review of 89 pregnant patients with pheochromocytoma showed a maternal mortality rate of 48\%.\textsuperscript{22} This study also demonstrated that, in the first or second trimester, presurgical therapy with alpha-blockers followed by surgical resection 2 weeks later brought down the maternal morbidity and mortality; however, fetal mortality remained high (67\%).\textsuperscript{23} Recently studies have shown that medical management with alpha-blockade and close blood pressure monitoring with deferral of surgery till after delivery may further reduce maternal and fetal mortality and morbidity.\textsuperscript{23} In our study, there was 1 pregnant patient with pheochromocytoma (late second trimester). The favorable maternal outcome in our case was related to a prompt control of blood pressure and medical termination of pregnancy followed by quick surgical extirpation of the tumor.

Patients with malignant pheochromocytoma form another group, the management of which is difficult. Therapy for malignant pheochromocytoma revolves around surgical removal and chemotherapy with cycles of alkylating agents, vinca alkaloids and dacarbazine. This combination has shown a complete tumor response of 100\%. There were 6 tumors (20\%) located extra-adrenally. Extra-adrenal pheochromocytomas account for approximately 11\%–27\%.\textsuperscript{9,12,13} of all pheochromocytomas and less than 1\% of these arise in the bladder wall from the sympathetic nervous system.\textsuperscript{21} Bladder tumors are usually localized to the trigone and such patients give a characteristic history of adrenergic symptoms on micturition, which was the case in our patient.

Conclusions: Our study of patients with pheochromocytoma has shown a higher incidence of symptoms such as headache, diaphoresis and flushing compared to studies from the West. The typical triad of headache, diaphoresis and flushing occurred in 26.7\% of cases only. Thus, investigations for pheochromocytoma should be carried out in all young hypertensive patients. In these patients, with control of blood pressure using adrenergic receptor blockade followed by surgical removal, a successful outcome and cure of hypertension can be achieved.

References

19. Stewart BH, Bravo EL, Haaga J, Meaney TF, Tarazi R. Localization of
Endomyocardial Fibrosis is Associated with Selective Deposition of Type I Collagen

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Background: Endomyocardial fibrosis is a distinct form of heart disease leading to restrictive ventricular filling and cardiac failure. The disease is characterized by a marked thickening of the endocardium due to the deposition of dense fibrous tissue composed of wavy bundles of collagen. Changes in collagen composition and an abnormal increase in its concentration result in a stiffer myocardium and ventricular diastolic dysfunction. The nature of cardiac collagens and the relative proportions of collagen types in endomyocardial fibrosis have not been documented in the literature.

Methods and Results: This study analyzed collagen composition in the cardiac tissues of 13 patients with endomyocardial fibrosis and 6 individuals who were the victims of traffic accidents or suicidal deaths and did not have any heart disease. We estimated the relative proportions of types I and III collagen after pepsin digestion of the tissue and separation of the emerging peptides by sodium dodecyl sulfate polyacrylamide gel electrophoresis. The mean type I:III collagen ratio was 0.51±0.06 in normal individuals, and 0.93±0.43 in patients with endomyocardial fibrosis (p<0.05). The alteration in the type I:III collagen ratio was due to a disproportionate increase in type I collagen.

Conclusions: The results indicate that a selective increase in type I collagen may contribute to the impaired diastolic distension of the ventricles in patients with endomyocardial fibrosis. (Indian Heart J 2001; 53: 486-489)

Key Words: Endomyocardial fibrosis, Cardiomyopathy, Collagen phenotype
were done following the methods described by Mukherjee and Sen. Specimens collected were labeled and stored at −20 °C till analysis. Before analysis, the tissues were minced with scissors, lyophilized and the dry weight taken. The lyophilized material was then pulverized and samples were initially extracted for 24 hours at 4 °C, with 1M NaCl in 0.05 M tris buffer, pH 7.4, containing protease inhibitors such as ethylenedinitrilo tetra-acetic acid (EDTA) 20.0 mM, di-isopropyl flurophosphate (DFP) 1.0 mM, N-ethyl maleimide (NEM) 2.0 mM and pepstatin 1 µg/ml. The supernatant was retained along with all the supernatants of subsequent 24-hour re-extractions with 0.05 M acetic acid at 4 °C. Samples were digested 3 times successively, each time for 24 hours’ duration with pepsin (1 mg/1ml) in 0.5 M acetic acid. The extracts were pooled and collagen precipitated by adding NaCl to a final concentration of 2 M at 4 °C.

Biochemical analysis: The collagen precipitate collected by centrifugation was re-dissolved in 0.5 M acetic acid and dialyzed against 0.02 M dibasic sodium phosphate. In these samples, collagen types were identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Different lanes of gel were loaded with 100 µg of standard types I and III collagen and 100 µg of each of the extracted heart collagens. After electrophoresis, the gels were stained with Coomassie blue R250 and destained using a solution of acetic acid and methanol. The stained gels were scanned at a wavelength of 530 nm using a soft laser scanning densitometer gel scanner. Relative amounts of types I and III collagen were estimated by determining the peak areas distinctive for collagen types, and the relationship between these areas and the amount of collagen applied to the gel. Concentrations of types I and III collagen in tissues were calculated from the regression equation of the standards. Standard types I and III collagen were procured from SIGMA.

Group comparison was done using the Student’s t test.

Results
Concentrations of types I and III collagen were calculated after quantification of the pepsin fragments representative of each type. The total collagen concentration in the tissue extract was determined by the estimation of hydroxyproline in 100 µg of tissue collagen from each sample loaded in SDS-PAGE gels.

Hearts with EMF had significantly increased type I collagen concentration (68.64±24.19 µg) when compared with that of control samples (43.94±19.5 µg) (p<0.05), while type III collagen concentration in hearts with EMF and control samples were not significantly different (79.42±22.70 µg and 87.6±38 µg, respectively). The type I:III collagen ratio was 0.51±0.06 in normal hearts and 0.93±0.43 in hearts with EMF (p<0.05). The results are summarized in Table 1.

Table 1. Type I:III collagen ratio in normal hearts and hearts with EMF together with mean values for types I and III collagen in densitometric scans

<table>
<thead>
<tr>
<th>Collagen (µg)</th>
<th>Normal hearts (n=6)</th>
<th>Hearts with EMF (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>43.94±19.5</td>
<td>68.64±24.19*</td>
</tr>
<tr>
<td>Type III</td>
<td>87.6±38.0</td>
<td>79.42±22.70</td>
</tr>
<tr>
<td>Type I:III ratio</td>
<td>0.51±0.06</td>
<td>0.93±0.43*</td>
</tr>
</tbody>
</table>

*p<0.05

To validate our procedure, we loaded 3 lanes of the gel: the first with 25 µg of collagen standard, the second with 25 µg each of collagen standard and heart collagen, and the third with 25 µg heart collagen, and estimated the percentage of recovery. The results are shown in Table 2.

Table 2. Data on validation of collagen quantification

<table>
<thead>
<tr>
<th>Collagen</th>
<th>Area under peak (cm²)</th>
<th>Predicted correlation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 µg collagen standard</td>
<td>10.0</td>
<td>22.5</td>
</tr>
<tr>
<td>25 µg collagen standard+25 µg heart collagen</td>
<td>29.5</td>
<td>22.5</td>
</tr>
<tr>
<td>25 µg heart collagen</td>
<td>20.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

The relationships between peak area and types I and III collagen concentrations are shown in Fig. 1. Figure 2 is a representative densitometric scan of the gels. Small quantities of types V and VIII collagen were also seen. However, their contribution to the total collagen concentration was negligible. The lack of correlation between the age of the patients and percentage of type I collagen in both the groups of patients is seen in Fig. 3.

Discussion
The present study aimed to examine the relative proportion of the major collagen types in the ventricular tissues of patients with EMF. Cardiac tissues obtained from patients with EMF were compared with those obtained from normal subjects. The ratio of different collagen types was estimated by SDS-PAGE after solubilization of collagen molecules by
Collagens constitute the major structural proteins of the interstitium of the heart, which, in turn, forms a support for other myocardial structures. The two most abundant collagen types in the human myocardium are types I and III. Type I collagen fibers have a substantial tensile strength whereas type III fibers possess a resistance that is ideal for maintaining the structural integrity and distensibility of the network. The relative proportion of these collagens may, therefore, play an important role in determining the physical properties of the extracellular matrix. Recently, it has been recognized that while cardiac myocytes and the coronary vasculature are central to the contractile function and viability of the myocardium, so is the extracellular matrix or cardiac interstitium and, in particular, the constituent types I and III fibrillar collagen matrix. A biochemical defect within this collagenous network or its physical interruption has the potential to adversely alter the tensile strength and tethering support function, thereby altering the architecture and mechanical properties of the myocardium. Collagen plays an important role not only in the mechanical properties of the heart but also in maintaining an even myocardial shape.

In pathological conditions, remodeling of the collagen matrix occurs both in terms of structure and biochemistry. Collagen phenotypes have been well characterized in pathological conditions such as cardiac hypertrophy secondary to systemic hypertension, dilated cardiomyopathy and ischemic cardiomyopathy. The concentration of myocardial collagen increases three- to six-fold during hypertrophy secondary to valvular heart disease and systemic hypertension. An increase in type I:III collagen ratio has been reported in other myocardial diseases and dilated cardiomyopathy. Such an increase in collagen and the associated structural remodeling results in an altered myocardial function. Ischemic cardiomyopathy in humans is characterized by an increased deposition of type III collagen, without a change in type I collagen concentration, resulting in a decrease in the type I:III collagen ratio. Dilated cardiomyopathy is associated with an increase in the concentrations of both collagen types, predominantly type I collagen, resulting in an...
increase in the type I:III collagen ratio. Both these forms of cardiomyopathy are characterized by dilatation of the heart and poor systolic function.

The hallmark of EMF is contracted ventricles and altered myocardial diastolic function resulting from increased deposition of collagen in the endomyocardium. In the present study, we have shown that in patients with EMF, there is a quantitative increase in type I collagen concentration, resulting in an elevated type I:III collagen ratio. In an earlier study, Bolarin and Andy reported that enzyme levels of collagen biosynthesis are increased in patients with EMF, suggesting an enhanced collagen synthetic activity.

The abnormal increase in collagen concentration could account for the stiffer myocardium and ventricular diastolic dysfunction seen in EMF. Our findings suggest that EMF is not different from other myocardial diseases in this respect. Although the nature of the underlying changes in collagen metabolism in EMF remains unclear, alterations in both the synthetic and the degradative processes may be important.

In summary, this study demonstrates that there is an increase in the type I:III collagen ratio in patients with EMF. This alteration is similar to the observations made in other myocardial diseases. This is the first demonstration that EMF is associated with a distinct alteration in the composition of the interstitial collagens.

References

Percutaneous Transluminal Angioplasty with Cutting Balloon and Stenting for Isolated Bilateral Aorto-Coronary Ostial Stenosis in a Young Female

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Coronary artery disease involving both coronary ostia (left main and right coronary) is extremely rare in a premenopausal female, without pre-existing coronary risk factors. We report a case of tight bilateral coronary ostial disease which presented in unusual clinical circumstances in a young female, which was successfully revascularized by single-stage aorto-ostial cutting balloon angioplasty and stenting. (Indian Heart J 2001; 53: 490-492)

Key Words: Coronary ostial stenosis, Stenting, Cutting balloon

An isolated bilateral aorto-coronary ostial stenosis is a rare occurrence. Generally, lesions located within 3 mm of the origin of a vessel are considered ostial, but some authors consider lesions up to 5 mm from the origin as ostial. Besides atherosclerosis, aorto-coronary ostial lesions may occur uncommonly in various other disease states such as syphilis, Takayasu's arteritis, fibromuscular dysplasia and postradiation fibrosis. Cannulation of the coronary artery during aortic valve surgery, coronary angiography or angioplasty can also potentially lead to coronary ostial stenosis. A bilateral tight coronary ostial lesion is potentially lethal and can present as sudden cardiac death, myocardial infarction, angina or ischemic cardiomyopathy. An isolated ostial left main coronary artery (LMCA) stenosis and bilateral coronary ostial disease were earlier managed by conventional coronary artery bypass surgery (CABG). Surgical aorto-ostioplasty has also been successfully used for managing these conditions. With improvement in hardware and increasing experience, isolated ostial disease of the LMCA has been managed by stenting alone or debulking and stenting. A cutting balloon has been used for ostial lesions with or without stenting. However, the use of cutting balloon angioplasty and stenting has not been described for the management of isolated bilateral aorto-ostial coronary artery lesions. We report the case of a young female who had tight bilateral aorto-ostial coronary stenosis presenting with non-Q-wave anterior wall myocardial infarction, managed by cutting balloon angioplasty and stenting.

Case Report

A 23-year-old female, mother of a 3-year-old child, was hospitalized with unstable angina. She had a history of crescendo angina for the past 6 months. Her electrocardiogram (ECG) showed 3 mm ST segment depression in the anterior precordial leads during angina, the Trop-T test was positive and CPK-MB was mildly raised. Her hemogram, glucose tolerance test and renal profile were normal, but the erythrocyte sedimentation rate (ESR) was 76 mm and C-reactive protein (CRP) level was elevated. Serological tests for syphilis and autoimmune disease were negative and the lipid profile was well below the atherosclerotic risk range. Her echocardiogram showed mild aortic regurgitation (AR) and hypokinesia of the anterolateral wall with normal left ventricular (LV) systolic function. The coronary angiogram showed 90% discrete ostial stenosis of the right coronary artery (RCA) and LMCA. The RCA was collateralizing with the left anterior descending (LAD) coronary artery (Fig. 1a and b). An LV angiogram exhibited mild hypokinesia of the anterolateral wall with normal LV systolic function and an aortogram revealed mild AR. The aortic lumen as well as carotid, subclavian and renal arteries appeared smooth and disease free. In view of her young age and severe symptoms, angioplasty and stenting of both ostia were planned.
She was pretreated with soluble aspirin and clopidogrel. The patient's consent was obtained for percutaneous transluminal coronary angioplasty (PTCA) and stenting of the lesions. The procedure was performed under narcotic sedation and local anesthesia with monitored anesthetic care and intra-aortic balloon pump (IABP) standby.

**Technique:** A 7 F conventional arterial sheath was placed percutaneously in the right femoral artery. The left coronary ostium was partially engaged with a 7 F JL 3.5 short-tip guiding catheter as there was a marked fall in blood pressure and angina with full engagement. As the patient had significant angina, 3 mg intravenous (i.v.) metoprolol was given. The patient was heparinized with 12 500 units of heparin. A 0.014" floppy-tipped guidewire was used to cross the lesion, keeping the wire tip in the distal LAD. The lesion was predilated with a 3.5×10 mm cutting balloon at 6–8 atm for 10–15 s, and stented with a 10 mm Prolink stent mounted on a 3.5×10 mm balloon. The stent was placed very carefully to ensure optimal ostial coverage with minimal protrusion of the stent into the aorta. The guiding catheter was further disengaged by pushing the guidewire deeper during positioning of the stent. A deployment pressure of 12 atm was used. The stented segment was postdilated with the guiding catheter disengaged using a 4×9 mm balloon at 14 atm. There was no residual stenosis or dissection after postdilatation (Fig. 2a). The right coronary ostium was partially engaged with a 7 F JR 3.5 guiding catheter. The lesion was crossed with a 0.014" floppy-tipped guidewire, keeping the wire tip in the distal posterior descending artery (PDA). The ostial lesion of the RCA was dilated with a 3.5×10 mm cutting balloon at 6–8 atm. The RCA ostium was then stented with a 10 mm stent mounted on a 3.5×10 mm balloon, ensuring optimal ostial coverage with the stent. During placement of the stent, the guiding catheter was disengaged into the aorta by pushing the guidewire deeper. The end result was good with no residual dissection or stenosis (Fig. 2b). At 2-month follow-up, the patient was asymptomatic.

**Discussion**

Coronary ostial stenosis involving both the coronary ostia is a rare occurrence. There have been few reports of bilateral coronary ostial stenosis in young subjects without known conventional coronary risk factors. In the absence of conventional coronary risk factors, coronary ostial narrowing has been reported in fibromuscular dysplasia, syphilitic aortitis, postradiation and Takayasu's arteritis or without any recognizable etiological background.3–7

Our patient was a menstruating young woman without any previous illness or conventional atherosclerotic risk factors, who presented with progressive angina culminating in an acute coronary syndrome. Serological tests for syphilis were negative. The elevated ESR and CRP in the setting of minimal myocardial necrosis did not point to a specific etiology. However, in the setting of a mild aortic regurgitation, the aforementioned condition could occur in Takayasu's arteritis. Currently, the diagnosis of Takayasu's arteritis is based on the typical distribution of vessel involvement, elevated surrogate inflammatory markers in the serum and response to anti-inflammatory therapy. The major limitation in the diagnosis of Takayasu's arteritis is the absence of specific tests.

Tight bilateral ostial stenosis of the coronary arteries poses an imminent risk of sudden death due to global ischemia or infarction.1 This is a clinical emergency from the therapeutic viewpoint. The choice of therapy in aorto-ostial stenosis of the coronary artery has conventionally been CABG or surgical patch aorto-coronary ostioplasty.3–9

Aizawa et al.3 reported a patient with syphilitic aortitis and bilateral coronary ostial stenosis managed by CABG. Borolotti et al.9 reported their experience with four patients in whom surgical ostio-aortoplasty was carried out for isolated coronary ostial stenosis.

There were major concerns with a surgical approach in our patient. Apart from the young age of the patient, the risk of progressive involvement of the aorta and its branches in aortoarteritis could compromise distal coronary
perfusion. Surgical aorto-coronary ostioplasty in an inflamed vessel also had the potential of restenosis in the surgical sites.

Stenting the ostium of the LMCA with or without debulking is an attractive and less invasive option with low procedural risk and acceptable intermediate- and long-term results in atherosclerotic coronary artery disease. However, the role of stenting in nonatherosclerotic aorto-ostial stenosis finds little mention in the literature. Lee reported successful performance of PTCA of the LMCA ostium in Takayasu’s arteritis. Park et al. and Silvestri et al. reported stenting of the LMCA with a high success rate. Debulking with directional coronary atherectomy and stenting of the LMCA has been described for a large LMCA (>3.5 mm). There is no significant difference in the restenosis rate between stenting with or without debulking for LMCA stenosis.

Cutting balloon angioplasty works on the principle of producing minute longitudinal incisions in the wall of the vessel. Radial dilatation of the vessel after producing these incisions has the potential of better plaque compression without extensive plaque contusion or dissection. Vessel recoil is less, making this an ideal form of balloon angioplasty in ostial lesions.

Since restenosis following stenting for non-atherosclerotic coronary disease is not well understood, we recommend a longer and more frequent follow-up in this situation.

For isolated bilateral coronary ostial lesions, PTCA using a cutting balloon followed by stenting is technically feasible. Early experience in this rare clinical condition suggests that this technique is safe and effective. At present, there is a paucity of data to show the long-term viability of this treatment method. Further studies are needed before its advantage over surgery—especially surgical ostioplasty—is established.

References
Transcatheter Closure of a Large Coronary Artery Fistula with Amplatzer Duct Occluder: A New Approach

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We report a new retrograde approach for the successful closure of a large right coronary artery fistula in a 27-year-old man using the Amplatzer duct occluder. The device was deployed through a coronary angioplasty-guiding catheter that had been advanced through the aorta and the dilated right coronary artery into the fistula. This method simplified the procedure by eliminating the need for making a femoral artery-to-femoral vein wire loop. (Indian Heart J 2001; 53: 493-495)

Key Words: Catheter intervention, Coronary anomaly, Amplatzer device

Coronary artery fistulae (CAF) are characterized by abnormal communication between a coronary artery and a cardiac chamber or vessel. Often they are detected as an incidental finding in an asymptomatic patient with a murmur. When the flow through the fistula is large, CAF can cause heart failure, coronary steal and myocardial ischemia, progressive enlargement and rupture, arrhythmia or infective endocarditis.1-3 Closure is indicated for large CAF to prevent complications. As transcatheter techniques continue to evolve, nonsurgical closure of unnecessary vascular structures including CAF is becoming more common using Gianturco coils, interlocking detachable coils, detachable balloons, polyvinyl alcohol foam or Rashkind’s double umbrella.4-9 Recently, the Amplatzer duct occluder (ADO) has been used to close CAF using a femoral artery-to-femoral vein wire loop for deploying the device in the fistula.10-13 To our knowledge, the following case represents the first report of an ADO being deployed in a CAF by the retrograde arterial approach using a coronary angioplasty-guiding catheter.

Case Report

SK, a 27-year-old male, was found to have a continuous murmur when examined for atypical chest pain and fatigue. The murmur was best heard along the right sternal border. The chest X-ray showed mild cardiomegaly with prominent pulmonary vascular markings, but the electrocardiogram (ECG) was normal. On two-dimensional echocardiography, the right atrium (RA) and right ventricle (RV) were enlarged. Doppler echocardiography showed a continuous flow into the upper part of the RA. A right coronary artery (RCA)-to-RA fistula was suspected. Cardiac catheterization demonstrated a significant left-to-right shunt in the RA (Qp/Qs 1.7). The pressures in the pulmonary artery and left ventricle (LV) were normal. Aortogram and selective coronary angiograms were carried out. The proximal RCA was dilated (9 mm). A large tortuous fistula was seen to arise from the RCA proximal to the ventricular branches and run in a posterior direction to open high in the RA (Fig. 1). The mid-segment of the fistula showed a relatively narrow neck with an aneurysmal pouch (10 mm in diameter) distal to the neck (Fig. 2). The flow through the fistula was large while the RCA branches distal to the fistula filled very faintly. The left coronary artery and the LV were normal on angiography.

Because of the patient’s symptoms, significant shunt detected by oximetry and large size of the fistula, we decided to close it by the transcatheter method. The RCA was engaged with an 8 F multipurpose large-lumen coronary angioplasty-guiding catheter. A 0.035" Terumo guidewire was introduced through this catheter into the RCA and manipulated through the fistula into the RA. Keeping a generous loop of guidewire in the RA, the guiding catheter was gently and carefully advanced on the wire until its tip crossed the narrow neck of the CAF. The position and manipulation of the catheter was guided by small hand injections of contrast. An ADO (10-8 mm; AGA Medical Corp., Minnesota, USA) was loaded and introduced through the guiding catheter. At this stage, it was necessary to cut

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and shorten the guiding catheter so that the device could be delivered through it. The ADO was advanced into the fistula until its distal rim opened in the pouch beyond the neck. Initially the whole system and then the guiding catheter alone were slowly drawn back to deploy the occluder in a dumb-bell shape across the neck. Gentle push and pull on the delivery wire confirmed that the occluder was in a stable position. No symptoms, ECG or hemodynamic changes were noted and the murmur disappeared. After waiting for 10 minutes, the device was released. Repeat angiography showed complete closure of the CAF with improved flow and filling of the distal RCA and its branches (Figs. 3 and 4). Doppler echocardiography on the following day showed that the device was stable and there was no residual flow. At follow-up after 6 months the patient was well. His ECG was normal and Doppler echocardiography showed no shunt.

Discussion

This case demonstrates a simple and quick method of closing a large CAF through the retrograde arterial approach using an ADO. Earlier reports on the use of an ADO in CAF have described deployment of the device through the venous route. This necessitates a femoral artery-to-femoral vein guidewire loop for the introduction of a delivery sheath of appropriate size, which makes the procedure longer and more difficult.
In our case, the fistula originated from the proximal part of the RCA. Thus, it was possible to cannulate the fistula deeply without causing any major distortion or damage to the vessel. We preferred to use a coronary angioplasty-guiding catheter for delivery of the ADO because its softatraumatic tip and relative resistance to kinking are definite advantages over the Amplatzer delivery sheath. The anatomy of the CAF showed a favorable “neck”, which allowed us to deploy the occluder in a stable position, although the wide (aortic) end of the ADO was directed towards the distal part of the fistula. The large size of the fistula and the dilated pouch beyond the neck allowed the ADO to expand without causing excessive distention of the vessel. This was important because CAF often have thin walls that can rupture.

The course of the CAF suggested that it was in the atrial branch of the RCA. Closure did not produce any untoward hemodynamic or ischemic changes, and the rhythm remained normal. In fact, filling of the distal RCA branches improved substantially once the steal through the CAF was abolished. This method can be employed whenever the fistula is large and proximal in origin, allowing for safe passage of a relatively large delivery catheter or sheath. We anticipated difficulty in using this approach in small children or in cases where the CAF arises in the distal part of the coronary artery. Several occluding devices are available for closure of CAF. Coils and microparticle embolization are not suitable for large CAF due to the risk of incomplete closure and embolism.6-9,13 Detachable balloons and Rashkind’s double-umbrella device have been used in large fistulae but they need a large delivery sheath which can be introduced only over an arteriovenous wire loop.6-9 The ADO has several advantages such as a smaller delivery system, ability to recapture and reposition, and a high rate of complete closure.14

Conclusions: In this report, we have shown that selected CAF, especially if large and proximal in origin, can be successfully closed with an ADO through a simple retrograde arterial approach alone, using a coronary angioplasty-guiding catheter for delivery.
Pre-excitation with Syncope: A False Lead?
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An 18-year-old girl with pre-excitation presented with a history of recurrent syncope preceded by palpitation. The accessory pathway, which had a relatively long antegrade effective refractory period of 340 ms, was mapped and successfully ablated in the left lateral region. However, on subsequent procedures, she had reproducible sustained polymorphic ventricular tachycardia, which was found to be the cause of her syncope. Thus, alternate mechanisms of tachycardia need to be considered in patients with pre-excitation when the presentation is atypical. (Indian Heart J 2001; 53: 496-498)

Key words: Syncope, Pre-excitation, Ventricular tachycardia

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yncope, which accounts for 3% of emergency room visits and 6% of all hospital admissions, is an ominous symptom in patients with pre-excitation since it may indicate a higher risk for sudden death. We describe an interesting case of recurrent syncope in a young woman with pre-excitation.

Case Report

An 18-year-old female presented with a 4-year history of multiple episodes of paroxysmal palpitation. These were often accompanied by syncope lasting for a few seconds to minutes. She had experienced nearly 40 episodes of syncope over the past few years. Her basal electrocardiogram (ECG) demonstrated minimal pre-excitation, suggestive of a left-sided accessory pathway (AP) (Fig. 1a). There was no documented tachycardia. The clinical examination, chest X-ray and two-dimensional (2-D) echocardiographic examination were normal. Serum electrolyte levels and routine biochemistry were also within normal limits. The patient was not on any antiarrhythmic drugs prior to the electrophysiological study (EPS).

The syncopal episodes were thought to be related to the pre-excitation, either due to atrial fibrillation (AF) with rapid conduction over the AP or by rapid circus movement tachycardia leading to hemodynamic instability. She was taken up for EPS with a plan for radiofrequency ablation (RFA). Electrode catheters were placed in the coronary sinus, bundle of His and right ventricle via the femoral route. The basal intervals were: PR 118 ms; AH 74 ms; HV 19 ms; QRS 98 ms; and QT 346 ms. The ventricular stimulation protocol revealed eccentric retrograde activation earliest in the distal coronary sinus, confirming a left lateral AP. Atrial-and ventricular-programmed extra stimulation and continuous pacing protocols were performed at different cycle lengths. The antegrade and retrograde effective refractory periods (ERPs) of the AP were 340 ms and 300 ms, respectively. Nonsustained orthodromic tachycardia was inducible with atrial extra stimuli. Mapping was performed via the transaortic route with a 7F ablation catheter (Cordis-Webster). The earliest activation (~19 ms) was found in the left lateral region on the ventricular aspect of the mitral annulus. The pre-excitation disappeared immediately after starting the RF energy which was delivered for 60 s with a peak temperature of 60 °C and power of 48 Watts. The 12-lead ECG was normal after the procedure (Fig. 1b).

Surprisingly, the patient developed sustained spontaneous polymorphic ventricular tachycardia (VT) a few seconds later (Fig. 2). This VT persisted despite withdrawal of the catheters from the ventricles and terminated spontaneously only after 90 s. The systolic BP during VT was 70 mmHg. Since the refractory periods in the AP were relatively long, we considered the possibility of idiopathic polymorphic VT as the cause of syncope. Hence, a complete VT induction protocol was performed. Ventricular fibrillation (VF) was induced using three-programmed extra stimuli, each at a cycle length greater than 200 ms (Fig. 3), and was promptly defibrillated.

The patient was started on amiodarone (200 mg daily after and initial oral loading dose of 600 mg daily for 10
days) and atenolol (25 mg) prior to discharge. She was asymptomatic at 3-month follow-up.

**Discussion**

The prevalence of syncope in patients with Wolff-Parkinson-White (WPW) syndrome is about 20%.

Clinical VT is rare in patients with WPW syndrome and usually occurs in association with an underlying cardiac disease. Ventricular tachycardia causing syncope in patients with pre-excitation has rarely been documented by EPS. Wellens, while studying the electrophysiological properties of 322 patients with pre-excitation, found that only 2 had VT independent of their AP, confirming that this is a rare occurrence. Lloyd et al. reported 5 patients in whom EPS revealed VT rather than supraventricular tachycardia as the cause of syncope. However, nonsustained VT during programmed ventricular stimulation is a nonspecific finding and is not a marker of sudden cardiac death in patients with WPW syndrome.

In the present case, the antegrade refractory period of the AP was not short enough to explain the occurrence of AF which was rapidly conducted over the AP leading to VF, as a cause of syncope. Moreover, numerous episodes of syncope are extremely rare in WPW syndrome. On the contrary, the reproducible induction of polymorphic VT rapidly degenerating into VF was presumably the cause of the syncopal episodes. Idiopathic VT/VF is a rare but well documented cause of sudden death in young adults. The pre-excitation pattern was a false lead in our patient and the true cause of syncope was discovered fortuitously.

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Aneurysm of the Vein of Galen in Neonates: Report of Four Cases

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In neonates, aneurysm of the vein of Galen often masquerades as cyanotic congenital heart disease. We report 4 cases of neonates presenting with malformation of the vein of Galen at our institution. An increased awareness of this entity seems warranted. (*Indian Heart J* 2001; 53: 499-502)

**Key Words:** Aneurysm, Heart failure, Neonates

Heart failure and cyanosis in infants almost always results from congenital heart disease. Systemic arteriovenous malformations (AVMs) are a rare cause of such a presentation and the diagnosis is often missed. We report 4 cases of AVMs related to malformation of the vein of Galen who presented to us in the past five years. The purpose of this report is to highlight the clinical presentation and increase awareness of this entity. The clinical diagnosis was missed in the first case but correctly made in the 3 subsequent cases.

**Case Reports**

**Case 1:** A full-term male child presented at 5 days of age with severe congestive heart failure (CHF) and mild cyanosis. The peripheral pulses were bounding and there was no radiofemoral delay. The first heart sound was normal while the second had a loud pulmonic component. There was a grade 3/6 systolic murmur heard best in the pulmonary area. The electrocardiogram (ECG) showed evidence of biventricular hypertrophy while the chest X-ray showed cardiomegaly. Echocardiography did not reveal any structural anomaly except that the pulmonary venous drainage was not clearly visualized. On cardiac catheterization, the aortic root angiogram showed markedly enlarged and tortuous neck vessels, suggesting an intracardiac AVM. The diagnosis was confirmed on imaging the cranium (Fig. 1). On detailed clinical examination, a grade 2/6 systolic bruit that had been missed in the initial clinical evaluation was heard over the cranium.

![Fig. 1. Digital subtraction angiogram showing vein of Galen malformation (arrows), dilated carotid artery and jugular vein (arrowheads). AO denotes aortic arch.](image)

**Case 2:** A full-term male child presented at 2 days of age with severe CHF and mild cyanosis. His peripheral pulses were bounding in all four extremities. The first heart sound was normal while the second had an accentuated pulmonic component. There was a grade 3/6 systolic murmur heard best in the pulmonary area. Due to our experience with the previous patient who had a similar presentation, a cranial bruit was sought and found. The ECG showed evidence of biventricular hypertrophy while the chest X-ray showed cardiomegaly with increased pulmonary vascularity.
Echocardiography revealed dilated right heart chambers, a patent foramen ovale, mild tricuspid regurgitation and an enlarged superior vena cava (SVC) and arch of the aorta (Fig. 2). Pulse Doppler study of the SVC showed increased forward flow with normal flow in the inferior vena cava (IVC). Doppler study of the ascending aorta and carotid arteries showed continuous forward flow (Fig. 3) while that of the descending aorta suggested diastolic run-off. Real-time ultrasound examination of the cranium suggested malformation of the vein of Galen and a contrast-enhanced computed tomographic (CT) scan of the head revealed an aneurysm of the vein of Galen.

**Case 3:** A 6-day-old male child had a history of CHF and mild cyanosis from the first day of life. His clinical findings were similar to those of the previous patients. The ECG was normal for his age while the chest X-ray showed cardiomegaly with increased pulmonary blood flow. Echocardiography, transcranial ultrasound and contrast-enhanced CT scan of the brain identified a malformation of the vein of Galen.

All three neonates succumbed to their illness within a week of being diagnosed.

**Case 4:** A 5-day-old child presented with findings similar to those of the 3 previous patients. Computed tomographic scan of the head showed a large malformation of the vein of Galen (Fig. 4). The parents were keen on aggressive treatment despite the poor prognosis. The patient was taken up for embolization of the feeding vessels using N-butyl cyanoacrylate. There was a decrease in the size of the aneurysm after embolization (Figs 5a and b) along with a marked improvement in CHF, and a significant reduction in cardiac size was seen in the chest X-ray (Figs 6a and b). However, the child succumbed to his illness the next day.

**Discussion**

Arteriovenous malformations are an uncommon cause of CHF in the neonatal period. Intracerebral AVMs being the most common amongst them. Although malformations of the vein of Galen constitute only 1% of all cerebral vascular

![Fig. 2. Two-dimensional echocardiogram showing enlarged arch of aorta (AO) and arch vessels. PA: pulmonary artery; CC: left common carotid artery.](image)

![Fig. 3. Pulse Doppler echocardiogram with cursor in the carotid artery showing continuous antegrade flow.](image)

![Fig. 4. CT scan of the cranium showing vein of Galen malformation (white arrows), dilated lateral ventricles (black arrows), periventricular calcification (black arrowheads) and changes of encephalomalacia in both cerebral hemispheres.](image)
malformations, they comprise up to 30% of all pediatric vascular malformations. The vein of Galen (formed from the median vein of the prosencephalon) is formed by the union of the two internal cerebral veins and goes on to drain into the straight sinus. An AVM occurs when the vein of Galen has an arterial input from one or more major intracranial arteries, either directly or via an interposed angiomatous malformation.

Symptoms and clinical signs vary with the age at presentation. In the newborn, the commonest mode of presentation is intractable heart failure. The malformation is more extensive in these infants as they receive inputs from numerous arterial feeders, and the prognosis is extremely poor with almost 100% mortality. In infants with a lesser degree of shunt, the clinical picture is that of an enlarging head (due to both obstructive and nonobstructive hydrocephalus) and mild heart failure. Older children and adults may present with focal neurological signs, developmental delay, seizures, headache or subarachnoid hemorrhage.

Diagnosis confusion in the neonate arises from the combination of severe CHF and cyanosis, pointing towards a cardiac disorder. Cyanosis results from the torrential venous return crossing the patent foramen ovale and a diagnosis of persistent fetal circulation may be considered by the unwary. Detailed clinical examination, however, reveals evidence of high-output heart failure and a cranial bruit (up to 80% of the cardiac output can be directed towards the cerebrovascular bed due to low resistance within the vascular malformation). Brisk upper limb pulses in the presence of severe heart failure should suggest the possibility of an AVM. Lower limb pulses may be relatively feeble due to steal by the cerebral fistula. In the extremely sick child, however, all pulses may be feeble. Although a benign systolic bruit is described in up to 15% of normal neonates and children, the presence of a systolic bruit over the cranium in a child with CHF should strongly suggest this disorder. All 4 of our patients had a systolic bruit over the cranium.

Two-dimensional echocardiography usually reveals normal cardiac anatomy with dilated right heart chambers and an enlarged SVC and arch vessels. Uncommonly, structural heart disease has been reported in these infants including coarctation of the aorta, atrial septal defect, ventricular septal defect and partial anomalous pulmonary venous drainage. Pulse Doppler echocardiography of the arch vessels demonstrates a continuous forward flow of high velocity which reflects the low peripheral resistance bed introduced by the AVM. High-velocity forward flow in the SVC with normal flow in the IVC are also seen. These features, in the absence of aortic regurgitation and a patent ductus arteriosus, suggest the extracardiac nature of the lesion and its intracerebral location. Transcranial ultrasonography is extremely useful in demonstrating the AVM while Doppler studies aid in demonstrating the flow in it. A semi-quantitative measurement of flow in the feeding and draining vessels can also be obtained. Color Doppler echocardiography helps to demonstrate the turbulent flow within the aneurysm. In addition, contrast venous echocardiography has been shown to be of use as the rapid return of microbubbles into the SVC is a pathognomonic sign of an intracerebral AVM in the absence of another peripheral left-to-right shunt in the upper part of the body. The contrast can be injected into a peripheral leg vein (which then crosses over from the right to the left across a patent foramen ovale) or directly into the aorta through an umbilical artery catheter.

Although CT scan of the brain demonstrates the AVM and visualizes the feeding vessels, the details thus obtained may not be sufficient to guide surgical treatment.
Computed tomography also depicts associated brain lesions such as calcification and anoxic brain damage. Magnetic resonance imaging (MRI) is superior to CT in its ability to demonstrate vascular anatomy, though it is unlikely to supplant angiography in the immediate future since sufficient details of arterial and venous anatomy which permit precise endovascular/surgical therapeutic decisions are usually not obtained. Prenatal diagnosis of this disorder is also possible and one can precisely delineate the vascular malformation.

Embolization of the feeding arteries of the AVM (in a single or staged sitting) is the preferred therapeutic modality for a patient in severe CHF. Transarterial embolization is the preferred route although transvenous and transocular routes have also been used. Solid materials, including microcoils (mostly fibered or unfibered platinum coils), microballoons and silk sutures have been used to embolize these vessels, with variable success. Liquid adhesives that have been used for embolization include cyanoacrylate monomers such as I-butyl cyanoacrylate and N-butyl cyanoacrylate, and polymers such as ethylenevinyl alcohol copolymer.

Even partial reduction in cerebral flow after embolization is sufficient for controlling CHF in the neonate as it permits retrograde thrombosis of the AVM. The mortality rate in neonates remains extremely high (up to 55%) even after embolization, partly due to the large extent of the malformation. Some recent reports have, however, indicated better immediate neonatal outcome. Embolization promptly alleviates the massive intracranial arteriovenous shunting and improves CHF. In infants in whom endovascular therapy is delayed, clinical results may be poor despite obliteration of the aneurysmal malformation. This is believed to be the result of an acquired occlusive venopathy affecting the dural venous sinuses due to high flow. Gamma knife surgery is not a viable option in the neonate as it does not produce any immediate reduction to high flow. 

In conclusion, aneurysm of the vein of Galen, a rare cause of cyanosis and heart failure in infants, can be diagnosed clinically in the appropriate setting. The extensive distribution of the aneurysm usually precludes surgical management/endovascular therapy.

References

Congenitally Unguarded Tricuspid Valve Orifice with a Giant Right Atrium and a Massive Clot in an Asymptomatic Adult

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An unguarded tricuspid valve is a rare congenital anomaly described in only a few antemortem case reports.\textsuperscript{1–9} It is a variant of tricuspid valve dysplasia wherein there is partial or complete agenesis of the tricuspid valve tissue.\textsuperscript{2} The leaflets are normally inserted on the ring and there is variable dysplasia of the chordae tendineae and papillary muscles. Most of the cases reported in the literature are associated with pulmonary atresia. An unguarded tricuspid valve orifice with a patent right ventricular outflow tract and dilated right ventricle is uncommon and needs to be differentiated from the more common entity—Ebstein’s anomaly of the tricuspid valve. The clinical presentation is usually in early childhood with cyanosis and/or congestive heart failure but there are a few patients in whom decompensation occurs during adult life with right ventricular failure and tricuspid regurgitation.\textsuperscript{7–9}

The natural outcome, with or without medical treatment, is not too dismal and one such patient survived till the age of 53 years.\textsuperscript{7} The advent of echocardiography has resulted in the diagnosis of a significant number of such patients, some of whom may present with associated atrial fibrillation.\textsuperscript{8,9} This report describes an asymptomatic young man who on echocardiographic examination showed a large right atrial clot, intense spontaneous echo contrast and a giant right atrium in association with an unguarded tricuspid valve orifice.

Case Report
A 25-year-old asymptomatic young man was evaluated by echocardiography because of abnormal findings on a 12-lead electrocardiogram (ECG) and chest X-ray. He denied the presence of any symptoms on exertion. Physical examination revealed a healthy, afebrile young man with a supine blood pressure of 112/76 mmHg, a pulse rate of 76 beats/min, irregular rhythm and elevated jugular venous pressure. Mild pretender hepatomegaly was present and precordial examination revealed faint heart sounds with a wide, variably split second sound and a grade 2/6 basal ejection systolic murmur. Hematological parameters and serum biochemistry were normal. A 12-lead ECG revealed atrial fibrillation with an average ventricular rate of 68 beats/min, complete right bundle branch block and nonspecific ST–T-wave changes. A plain chest X-ray showed cardiomegaly (cardiothoracic ratio—70%) and oligemic lung fields.

Two-dimensional echocardiography (Fig. 1) showed an elongated left atrium and a small left ventricle with paradoxical ventricular septal motion. The right atrium was dilated (12×10 cm) with intense spontaneous echo contrast and a large mobile thrombus (6×5 cm) was attached to its free wall. The septal leaflet of the tricuspid valve was intact and normally inserted, but the anterior and posterior tricuspid leaflets and the subvalvar apparatus were not visible. The inferior vena cava was dilated and showed no respiratory variation, while the right ventricular outflow tract was dilated with normal pulmonary arteries. Doppler interrogation of the right ventricular inflow and outflow tracts showed a low-velocity, to-and-fro flow with a peak velocity of less than 1 m/s. The patient declined further investigation and surgery.

Key Words: Congenital heart defects, Echocardiography, Thrombosis
Congenitally unguarded tricuspid orifice is a rare anomaly and antemortem diagnosis has been reported in the literature in about 17 cases only. An isolated unguarded tricuspid orifice with no other congenital abnormality has been reported in a few patients so far. No case of an asymptomatic patient surviving till adulthood has been reported. A giant right atrium with thrombus and spontaneous contrast, in the absence of any history of right heart failure and the presence of atrial fibrillation, are unique features of the case we studied. Atrial fibrillation has been reported in two of seven adult patients in a previous series reported by us.

Partial or complete absence of tricuspid valvar tissue diagnosed on fetal echocardiography was labeled as unguarded tricuspid valve orifice by Kanjuh et al. in 1964. This condition needs to be differentiated from Ebstein's malformation, tricuspid dysplasia in association with pulmonary atresia and intact ventricular septum, and Uhl's anomaly. Dysplasia of the leaflets along with displacement of the septal leaflet is an integral part of Ebstein's malformation. However, the mural leaflet is always present unlike in unguarded tricuspid orifice, in which case it may be completely absent. Pulmonary atresia with an intact interventricular septum may be associated with a variable degree of tricuspid valve dysplasia but it needs to be differentiated from Ebstein's malformation or an unguarded tricuspid orifice in which the right ventricle is dilated. The tricuspid valve is structurally normal in Uhl's anomaly. Dysplasia of the tricuspid valve is probably the most common cause of isolated tricuspid regurgitation and the unguarded tricuspid orifice is its most extreme form.

Because of the poor right ventricular contractile function, pulmonary circulation is maintained by the pumping action of the right atrium or the outflow tract. As observed in our patient, the right atrium can assume enormous proportions. Right-to-left shunting can occur through the patent foramen ovale. In some of these cases, functional pulmonary atresia can result from a combination of a severely abnormal tricuspid valve and markedly depressed right ventricular contractility. Unrecognized infective endocarditis is unlikely to be the cause of an unguarded tricuspid valve, as it is very difficult for such an extensive destruction to remain subclinical. The absence of vegetations goes against this diagnosis.

The natural history of this entity is variable. Several patients with a mild degree of right ventricular dysfunction survive to adulthood and even reach old age. Such patients tolerate tricuspid regurgitation well and become symptomatic only when significant right ventricular dysfunction sets in, with or without atrial fibrillation. This makes surgical treatment a difficult option since surgical results are not encouraging.

Discussion

Congenitally unguarded tricuspid orifice is a rare anomaly and antemortem diagnosis has been reported in the literature in about 17 cases only. An isolated unguarded tricuspid orifice with no other congenital abnormality has been reported in a few patients so far. No case of an asymptomatic patient surviving till adulthood has been reported. A giant right atrium with thrombus and spontaneous contrast, in the absence of any history of right heart failure and the presence of atrial fibrillation, are unique features of the case we studied. Atrial fibrillation has been reported in two of seven adult patients in a previous series reported by us.

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Isolated Cardiac Aspergillosis

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A 40-year-old man, a known case of Wolff-Parkinson-White syndrome, was admitted to the hospital in an unconscious state. In spite of medical treatment, the patient died within two hours of admission. At autopsy, the deceased was found to have aspergillosis involving the interatrial septum, aortic valve and root of the aorta. The rest of the organs were unremarkable. The patient did not show any obvious signs of being immunocompromised. We report this case of isolated cardiac aspergillosis in an apparently healthy individual. (Indian Heart J 2001; 53:505-507)

Key Words: Cardiac aspergillosis, Wolff-Parkinson-White syndrome, Infection

Invasive aspergillosis commonly occurs in immunocompromised individuals, the lung being the commonest site involved.1,2 Isolated involvement of extrapulmonary organs such as the heart has rarely been documented in the literature.2,3 We report a rare case of isolated cardiac aspergillosis involving the interatrial septum, aortic valve and root of the aorta in an 'apparently healthy' individual, where the diagnosis could be made only on autopsy.

Case Report

This 40-year-old male was admitted in an unconscious state to the cardiology department with complaints of dyspnea and palpitation for the past three days. The patient was diagnosed at another hospital as a case of Wolff-Parkinson-White (WPW) syndrome two years earlier for which he was treated intermittently. Previous records were not available. On clinical examination, the patient was found to be cyanosed, dyspneic with a pulse rate of 240 beats/minute. His blood pressure was 90/60 mmHg and the jugular venous pressure was raised. Cardiac auscultation revealed marked tachycardia and chest auscultation showed signs of pulmonary edema. There was a nontender hepatomegaly 3 cm below the costal margin. The electrocardiogram revealed a heart rate of 250 per minute, a broad QRS complex and left axis deviation. Echocardiography revealed an enlargement of both the ventricular chambers, moderate aortic regurgitation with pulmonary arterial hypertension. The left ventricular systolic function was found to be reduced.

The patient was diagnosed clinically as a case of WPW syndrome with atrial flutter. He was treated with direct current cardioversion, and injections of dopamine, heparin and furosemide. In spite of the medical treatment, terminally the patient developed bradycardia and died of cardiac arrest within two hours of admission to the hospital. A thoracoabdominal autopsy was performed.

Autopsy findings: The heart weighed 350 g and was unremarkable externally, with no evidence of a pericardial effusion. On opening the right atrium, the smooth part of the septum, including the fossa ovalis, showed an elevated gray-white plaque-like lesion falling short of the tricuspid annulus. The lesion encroached into the superior vena caval orifice which was thus compromised. The interatrial septum measured 2.5 cm and was hard and thickened (Fig. 1). Grossly, the lesion mimicked a tumour and involved the anatomical sites for the sinoatrial (SA) and atrioventricular (AV) nodes. The right ventricle and pulmonary artery were unremarkable. The left atrium revealed a similar raised plaque-like area over the interatrial septum corresponding to the lesion on the right side. The mitral valve was unremarkable, but the left ventricle was mildly dilated. The aortic valve cusps showed the presence of friable, red, angry-looking vegetations measuring 3-4 cm. The root of the aorta revealed the presence of friable hemorrhagic clots loosely adherent to the surface. Multiple sections were examined from both the atria including the interatrial septum, conduction system, ventricles, aortic valve and root of the aorta. Sections from the interatrial septum and the
plaque-like area in the right atrium showed widespread involvement of the myocardium with areas of necrosis and foreign body giant cell reaction (Fig. 2). There were numerous septate fungal profiles with parallel walls and acute angle branching which were better elicited by periodic-acid Schiff (Fig. 3) and Grocott silver methenamine stains. Many giant cells showed the presence of fungal fragments within their cytoplasm. A section from the aortic vegetation revealed similar fungal profiles within a fibrin meshwork. There was a contiguous spread to the root of the ascending aorta. Sections taken from the areas of the SA node, AV node and internodal region showed widespread replacement by the fungal granuloma. The diagnosis of aspergillosis of the interatrial septum, aspergillus endocarditis of the aortic valve and aspergillus aortitis of the root of the aorta was made. Meticulous gross and microscopic examination of the other organs failed to reveal any focus of fungal infection. The lungs had bilateral bronchopneumonia and the left kidney had a small area of infarction. Microscopic evaluation including special stains for fungi, done on lung and kidney sections, did not show the presence of fungus.

**Discussion**

Isolated cardiac aspergillosis is rare. Fisher et al. in a series of 91 cases of invasive aspergillosis, have documented a single case of a 78-year-old woman with sarcoma who developed nodal tachycardia and myocardial infarction several days prior to death. At autopsy, there was an aspergillus abscess in the interventricular septum. The disease has also been reported in a 15-year-old girl following an allogenic bone marrow transplantation. Both these cases had underlying risk factors which could be attributed to the occurrence of aspergillosis. In fact, invasive aspergillosis is known to occur in patients with a debilitating disease, on steroid therapy, cytotoxic drugs and antibiotics, or undergoing radiation therapy. Our case is unique as the patient did not have any such recognizable predisposing factors, and the development of invasive aspergillosis in an
otherwise healthy individual is extremely rare. An assessment of the neutrophil function in such a case may bring out subtle abnormalities of phagocytosis and impaired bactericidal activity which may contribute to a relatively immunodeficient state. In the present case, such investigations could not be carried out as the patient succumbed to the disease following emergency admission.

Though our patient was diagnosed as a case of WPW syndrome 2 years earlier, it is difficult to relate this clinical diagnosis with the autopsy finding of cardiac aspergillosis. Sections from the nodes and internodal areas showed the presence of fungal granuloma without any recognizable remnant of conduction tissue. It is possible that the patient initially had a cardiac arrhythmic disorder compatible with the WPW syndrome and a superimposed fungal infection was acquired later, before his demise.

The portal of entry for the fungus in the present case remains unknown. The possible sources include the lungs and the gastrointestinal tract. The lungs are the usual portal of entry for aspergillus, but in our patient there was no pulmonary involvement, though there was focal bronchopneumonia. However, multiple sections examined from these foci did not show any fungal profile.

Our patient also had aspergillus endocarditis involving the aortic valve, and this, together with the root of the aorta, showed destruction with numerous fungal profiles embedded in a fibrin-rich background. There was a paucity of inflammatory infiltrate within these vegetations, and a granulomatous reaction was conspicuous by its absence. It can be speculated, therefore, that the infective vegetations embolized in the intramyocardial artery and the organisms were lodged in the interatrial septum, evoking the subsequent granulomatous response. Aspergillus endocarditis is thought to be an opportunistic infection and can be seen in patients with a history of valvular cardiac surgery. The endocardial vegetations of aspergillus mural endocarditis are usually contiguous with the underlying myocardial infection. The mural endocardium overlying the interatrial septal lesion in the present case was unaffected, though the aortic valvular endocardium was involved by a noncontiguous spread.

The ante mortem diagnosis of cardiac aspergillosis is difficult to reach especially in a case like the present one, where the patient did not have any of the conventional predisposing factors. The diagnosis is often made at autopsy. It is possible that the infective fungal profiles are too large to traverse the systemic capillary bed and hence may not even enter the venous system. In such a case, fungemia is likely to be missed even if the venous blood is cultured. However, one needs to consider the diagnosis in a febrile, immunocompromised patient with unexplained cardiopulmonary decompensation, especially when the fungus is isolated or suspected to be the cause of infection elsewhere. Very rarely, the disease can primarily affect the heart in apparently immunocompetent individuals, thereby posing a diagnostic difficulty, as seen in our case.

References
Acute Reversible Left Ventricular Dysfunction Following General Anesthesia

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A acute reversible left ventricular dysfunction due to myocardial stunning is a known phenomenon during acute myocardial infarction, coronary angiography, coronary angioplasty or after coronary artery bypass surgery. We report a rare case of acute reversible dysfunction of the myocardium as a complication of general anesthesia in a patient with normal coronary arteries. This is a potentially fatal complication unless recognized early and treated aggressively. (Indian Heart J 2001; 53: 508–510)

Key Words: Myocardial stunning, Complications, Anesthesia

Case Report

A 45-year-old woman, mildly hypertensive with no other coronary risk factor and with a normal resting echocardiogram, was taken up for nasal polypectomy under general anesthesia. She was premedicated with 75 mg of pethidine intravenously (i.v.). General anesthesia was induced with i.v. pentothal sodium and vecuronium was used as a muscle relaxant. Endotracheal intubation was difficult and required three attempts which took about 2–3 minutes. Oxygen saturation ranged between 85% and 90% during this period. Soon after intubation, she had an episode of ventricular tachycardia which was converted to sinus rhythm with a bolus of 60 mg i.v. lignocaine. Within the next 5 minutes, she developed sinus tachycardia of 160 beats/min with an S3 gallop and hypertension (blood pressure 180/120 mmHg). She developed pulmonary edema, with frothy fluid gushing out of the endotracheal tube. There was a fall in systemic arterial oxygen saturation (SaO2 78%). Initially her oxygen saturation improved to 85% with 60 mg i.v. furosemide and a nitroglycerine drip at a rate of 5 µg/min. The systemic pressure fell to 70 mmHg systolic within 10 minutes of starting the nitroglycerine drip and she was put on inotropic support (dopamine 10 µg/kg/min and dobutamine 7.5 µg/kg/min). The electrocardiogram (ECG) taken within 15 minutes of the episode showed sinus tachycardia with no ST- or T-wave changes. Arterial blood gas (ABG) levels deteriorated and were: PaO2 54 mmHg; PaCO2 38 mmHg; and the pH was 7.210. At this stage, an echocardiogram revealed severe LV dysfunction (LV end-systolic dimension [LVESD]: 3.4 cm, and LV end-diastolic diastolic dimension [LVEDD]: 4 cm) with an akinetic anterior wall and dyskinetic interventricular septum. The left ventricular ejection fraction (LVEF) was 25% and there was mild mitral regurgitation (Fig. 1). She was shifted to the ICCU and a central venous pressure (CVP) line as well as an arterial line for pressure monitoring were established along with continued ventilatory and inotropic support. Her CVP was 10 mmHg. An ABG analysis after 3 hours of support showed improvement (PaO2 108 mmHg; PaCO2 32 mmHg; pH 7.350). Metabolic acidosis was
corrected by i.v. sodium bicarbonate. The systemic blood pressure was 96/50 mmHg and the urine output 40 ml/hour. The patient was put on L-carnitine. After 12 hours, she developed another bout of pulmonary edema while on maximal inotropic (dobutamine 15 µg/kg/min and dopamine 15 µg/kg/min) and ventilatory support. The systemic blood pressure was 60 mmHg (systolic), ABG measurements were: PaO2 64 mmHg; PCO2 40 mmHg and the pH 7.345. A repeat echocardiogram showed severe LV dysfunction involving all the segments with an LVESD of 3.5 cm; LVEDD of 3.9 cm and EF of 15%. At this stage, IABP support was initiated. She became hemodynamically stable with a mean arterial pressure of 82 mmHg and an augmented pressure of 106 mmHg. The ABG levels improved over the next 6 hours—PaO2, 124 mmHg, PCO2, 28 mmHg at an FIO2 of 80%. Cardiac enzyme levels were mildly elevated (CK 640 IU, CK-MB 32 IU) on the first day. Serial CK and CK-MB readings over the next two days were CK 210 IU and 146 IU, CK-MB 20 IU and 18 IU, respectively. Repeat echocardiograms over the next 4 days showed progressive improvement in LV contractility with more segments regaining normal contractility. Serial ECGs did not show any evolving changes of transmural MI. Small daily doses of 3.125 mg carvedilol and 0.25 mg of digoxin were added on the third day. She maintained stable arterial pressure and good urine output (50–60 ml/hour). By the fifth day, the LVEF improved to 45% (LVESD 3 cm, LVEDD 4.1 cm). Chest X-ray showed no evidence of pulmonary edema and she was weaned away from IABP support. By the seventh day, she was weaned away from the ventilator and inotropic support. At this time, the echocardiogram showed a normal-sized LV (ESD 2.8 cm; EDD 4 cm) with an EF of 50%. There was hypokinesia of the lateral wall and distal part of the septum. The ECG at this stage showed ST coving with T-wave inversion in leads I and aVL. The patient was fully ambulant with no cardiac symptoms by the tenth day. Her echocardiogram showed normal LV function with no regional wall motion abnormality (Fig. 2). A diagnosis of pheochromocytoma was ruled out by the estimation of urinary vanillylmandelic acid (VMA) and metanephrine, and a negative abdominal ultrasound for adrenal and para-aortic masses. Coronary angiography done after an interval of 3 weeks revealed normal epicardial coronary arteries. She was discharged on diltiazem and was doing well at 6 months follow-up with a normal ECG and echocardiogram.

**Discussion**

This 45-year-old woman with no significant coronary risk factor developed cardiogenic shock following endotracheal intubation for general anesthesia. This case was characterized by acute severe LV dysfunction in a previously normal heart with normal LV function. She developed transient hypertension and extreme sinus tachycardia followed by hypotension and pulmonary edema. The ECGs did not show any acute MI pattern (ST elevation) and there

Fig. 1. Two-dimensional echocardiogram (parasternal long axis view) showing end-systolic image of LV—dilated left ventricle with global hypokinesia and severe LV dysfunction (EF 15%).

Fig. 2. End-systolic image of LV on the seventh day (parasternal long axis view) showing improved LV function with LV size returning to normal (EF 50%).
was no significant elevation of cardiac enzyme levels, thus ruling out an acute transmural MI. The fact that the myocardial contractility improved slowly with inotropic support shows that the myocardium was metabolically active.

Stunned myocardium is characterized by reversible contractile dysfunction, when the myocardial blood flow is fully or almost fully restored. In this condition, no metabolic deterioration occurs during inotropic stimulation. If myocardial stunning is severe, involving large parts of the LV and thus impairing global LV function, it can be reversed with inotropic agents and procedures. Our patient required IABP support.

What is the trigger for acute LV dysfunction in these cases? In our case, no surgical procedure had been started; only endotracheal intubation was done which was preceded by the administration of pentothal sodium and vecuronium. However, intubation was not easy and required multiple attempts. A number of agents used during general anesthesia may have negative effects on myocardial contractility. Halothane and enflurane have mild negative inotropic effects, especially in pre-existing LV dysfunction. However, our patient did not receive any of these agents. Intravenous thiopental and methohexitol may also depress myocardial contractility in patients with impaired LV function or elderly subjects. Though our patient received i.v. pentothal, it is unlikely that this would have contributed to the LV dysfunction because prior LV function was normal.

In the absence of a specific myocardial depressant and as the patient had persistent sinus tachycardia with an initial elevation of blood pressure, we postulate that an acute hyperadrenergic state developed following endotracheal intubation. This could have produced transient severe coronary spasm resulting in global LV dysfunction and cardiogenic shock.

An increase in plasma adrenaline and noradrenaline concentrations has been observed following tracheal intubation and surgery. Oral premedication with metoprolol attenuates the hypertensive response to tracheal intubation and reduces arrhythmias and operative blood loss during hysterectomy. Post-tachycardia-related cardiomyopathy was considered a possibility, but the interval between the tachycardia and LV dysfunction noted by echo-cardiography was very short (15 minutes). Studies using ambulatory ECG monitoring have also demonstrated myocardial ischemia during tracheal intubation and extubation. There have been reports of intraoperative coronary spasm during noncardiac surgery and one of these cases required several hours to become hemodynamically stable. Since our patient had a normal coronary angiogram, coronary spasm is a possibility which might have resulted in acute ischemic LV dysfunction. Structure-independent epicardial vasospasm can be an important element in serious cardiac ischemic events, particularly the focal persistent vasospasms that occur without plaques or injury. There was a case report of a 23-year-old woman without previous CAD developing an acute non-Q MI and stunned myocardium following topical lignocaine and phenylephrine used during nasal septoplasty. However, our patient did not receive any topical nasal medication. The possibility of severe LV systolic dysfunction secondary to an acute increase in afterload (severe hypertension) was also considered. In this event, the systolic dysfunction should resolve within a few hours of correcting the hypertension.

Our patient required more than 96 hours of inotropic and IABP support which would indicate an ischemia-induced LV dysfunction. Sincethemajority of LV myocardial segments were involved in the dysfunction (akinesia, dyskinesia) and all of them returned to normal contractility, it would fit in with the phenomenon of “stunned myocardium”. Although acute MI due to anesthesia-induced coronary spasm has been reported, only a few cases of stunned myocardium have been reported so far following noncardiac surgery.

References

Interactions Between the Renin–Angiotensin System and Dyslipidemia: Relevance in Atherogenesis and Therapy of Coronary Heart Disease

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Hypercholesterolemia and hypertension are major risk factors for coronary heart disease, and both are often present in the same patient. It is thought that interactions between dyslipidemia and activation of neurohumoral systems such as the renin–angiotensin system (RAS) may not only explain the frequent coexistence of hypertension and dyslipidemia, but may also play an important role in the pathogenesis of atherosclerosis. Experimental data suggest that there is a correlation between the effects of angiotensin II (Ang II) and lipoproteins on atherogenic risk. Data from recent experimental and clinical studies suggest that the pathways by which Ang II and low-density lipoprotein (LDL)-cholesterol lead to vascular disease may frequently overlap. Interventions directed at lowering total cholesterol, LDL-cholesterol and triglyceride levels, and raising high-density lipoprotein (HDL)-cholesterol levels result in a reduction in cardiovascular events. Control of blood pressure results in a similar decrease in cardiovascular events. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin type 1 (AT1) receptor blockers modulate RAS and are beneficial in reducing cardiovascular events in patients with vascular disease. There is a suggestion that the combined use of cholesterol-lowering drugs along with agents that modulate RAS may have additive benefit.

In this review, we discuss the results of experimental and clinical studies on the interaction between RAS and dyslipidemia. These observations may have an impact on the therapy of patients with coronary heart disease.

Renin–Angiotensin System and Cholesterol Biosynthesis

Cholesterol accumulation in the macrophages and their transformation into foam cells are major events in the development of atherosclerosis. Cellular cholesterol accumulation can result from increased uptake of LDL or oxidatively modified forms of LDL, as well as by enhanced macrophage cholesterol synthesis. Using macrophages harvested from the peritoneum after injection of Ang II, Keidar et al. were able to demonstrate that Ang II dramatically increased macrophage cellular cholesterol biosynthesis with no significant effect on blood pressure or on plasma cholesterol levels. The ACE inhibitor fosinopril and the AT1 receptor blocker losartan decreased cholesterol biosynthesis in response to Ang II. Further, in cells that lack the AT1 receptor (RAW macrophages), Ang II did not increase cellular cholesterol synthesis. These observations confirm the role of the AT1 receptor in Ang II-mediated cholesterol synthesis by macrophages. Other studies by Nickenig et al. have shown accumulation of LDL-cholesterol in cultured vascular smooth muscle cells and this effect is mediated via AT1 receptor activation.

Angiotensin II-mediated increase in macrophage cholesterol influx has been demonstrated, and attributed to the oxidant stress contributing to and facilitating LDL oxidation by arterial wall components. Angiotensin II can also bind to LDL and form modified lipoprotein, which is taken up at an enhanced rate by the macrophages scavenger receptor, leading to cellular cholesterol accumulation. Li et al. studied the kinetics of oxidized LDL (ox-LDL) uptake in endothelial cells and observed that Ang II, in a concentration-dependent fashion, enhanced the uptake of I-125 labeled ox-LDL in these cells. The AT1 receptor blocker losartan, but not the AT2 receptor blocker PD 123319, blocked the enhanced uptake of ox-LDL.

Fluvastatin, a competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, blocks the stimulatory effect of Ang II on macrophage cholesterol biosynthesis. Further, Ang II has been shown to upregulate macrophage mRNA for HMG-CoA reductase. The biochemical site of action for Ang II along the cholesterol biosynthesis pathway is probably HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.
Thus it appears that stimulation of cholesterol biosynthesis in macrophages, uptake of LDL in smooth muscle cells and ox-LDL in macrophages and endothelial cells requires, or at least facilitated by, AT<sub>1</sub> receptor activation. In this process, alteration in the expression of HMG-CoA reductase may play an important role.

Renin–Angiotensin System, Dyslipidemia and Reactive Oxygen Species (ROS)

Griendling et al. first documented that Ang II increases nicotinamide adenine dinucleotide phosphate (phosphate) hydride (NADH/NADPH) oxidase activity in macrophages via AT<sub>1</sub> receptor activation. Increased oxidative stress is now regarded as an important feature of hypercholesterolemic atherosclerosis. In this context, antioxidants have been shown to reduce the extent of progression of atherosclerosis in experimental animals and, in some studies, in humans as well.

Warnholtz et al. studied superoxide production in the aorta of rabbits fed on a diet containing 0.5% cholesterol. In their first study, they looked at the effects of endothelium removal on vascular superoxide production in control and Watanabe rabbits (hypercholesterolemia secondary to an LDL receptor defect). The rate of superoxide production was increased approximately two-fold in aortic segments from Watanabe rabbits compared with rabbits fed a normal diet (controls). This increase in superoxide production was abolished by removal of the endothelium from the arterial segments. In these segments, NADH oxidase but not NADPH activity was significantly increased. These findings suggested that hypercholesterolemia is associated with increased superoxide production secondary to activation of vascular NADH oxidase. These authors then measured the effects of an AT<sub>1</sub> receptor blocker (Bay 10-6734) on superoxide production and NADH oxidase activity in aortas from the controls and rabbits fed a high-cholesterol diet. The administration of an AT<sub>1</sub> receptor blocker reduced superoxide production and inhibited NADH oxidase activity in cholesterol-fed animals. The investigators concluded that in hypercholesterolemic animals, NADH oxidase represents a major vascular source of superoxide and that increased vascular levels of Ang II may cause increased NADH oxidase activity. Hypercholesterolemia is associated with AT<sub>1</sub> receptor upregulation, endothelial dysfunction and increased NADH-dependent vascular superoxide production. The improvement in endothelial dysfunction, inhibition of the oxidase and reduction of early plaque formation by an AT<sub>1</sub> receptor antagonist suggests that Ang II-mediated superoxide production plays a crucial role in the early stage of atherosclerosis. Clinical and experimental studies have identified a marked attenuation in endothelium-dependent vasodilatation as one of the early stages in atherosclerosis. In some cases, this is related to enhanced inactivation of endothelium-derived nitric oxide (NO) by superoxide, rather than a consequence of decreased NO production. It is known that AT<sub>1</sub> receptor activation leads to membrane-associated NADH-dependent oxidase. Low-density lipoprotein enhances AT<sub>1</sub> receptor expression in cultured smooth muscle cells and atherosclerotic lesions are associated with increased ACE expression, which may serve as a source for local production of Ang II and, ultimately, increased stimulation of vascular superoxide production.

A number of studies have shown that AT<sub>1</sub> receptor blockade normalizes the activity of NADH oxidase, reduces plaque area and macrophage infiltration, and simultaneously improves the endothelial surface in animals fed a high-cholesterol diet. These findings suggest that RAS plays a pathogenic role in both the initiation and acceleration of the atherosclerotic process and that inhibition of RAS may benefit the treatment of this malady.

Long-term treatment with ACE inhibitors has been shown to improve endothelial vasomotor function in patients with coronary artery disease (Trial on Reversing Endothelial Dysfunction, TREND), possibly because of decreased superoxide-mediated inactivation of NO. Importantly, the benefits of ACE inhibitor therapy are more pronounced in patients with hypercholesterolemia.

Hypercholesterolemia and RAS activation

Experimental studies have shown that hyperlipidemia enhances RAS activity. All components of increased RAS activation have been identified in hyperlipidemic atherosclerotic lesions. These include, in particular, increased expression of ACE and AT<sub>1</sub> receptors. A number of recent studies of human atherosclerotic tissues have confirmed the upregulation of ACE and AT<sub>1</sub> receptors, particularly in the regions that are prone to plaque rupture. Importantly, these areas show extensive inflammatory cell deposits, macrophage accumulation and apoptosis.

In vitro studies have shown that incubation of vascular smooth muscle cells with LDL increases expression of AT<sub>1</sub> receptors. Li et al. examined the expression of Ang II receptors in human coronary artery endothelial cells, and observed that ox-LDL increases the mRNA and protein for AT<sub>1</sub>, but not AT<sub>2</sub>, receptors, implying that ox-LDL increases AT<sub>1</sub> expression at the transcriptional level. In this process,
activation of the redox-sensitive transcription factor NF-κB plays a critical role. To define the relationship of RAS and lipids in humans, Nickenig et al. administered Ang II in normocholesterolemic and hypercholesterolemic men, and found that blood pressure was increased in the hypercholesterolemic group and this response could be blunted by LDL-cholesterol lowering agents. Further, these investigators found that there was a linear relationship between AT₁ receptor density on platelets and LDL-cholesterol concentration in plasma. Treatment with statins decreased the AT₁ receptor expression in this study. Statin-mediated downregulation of AT₁ receptor expression has also been shown in vascular smooth muscle cells. A recent study has shown that statins directly decrease AT₁ receptor expression in endothelial cells. The expression of genes for chymases—enzymes by which Ang II can be formed independent of ACE activation—has been shown to increase in atherosclerotic lesions of the aorta of monkeys fed a high-cholesterol diet. The functional significance of chymase in the development of atherosclerosis, however, remains uncertain.

**Role of Ang II in Hypercholesterolemic Atherosclerosis**

Activation of RAS with formation of AngII and activation of Ang II receptors, particularly AT₁ receptors, has been implicated in the pathobiology of atherosclerosis, plaque rupture, myocardial ischemic dysfunction and congestive heart failure. Several studies show that ACE inhibitors decrease progression of atherosclerosis in a variety of animal species. Since a number of different ACE inhibitors exert similar anti-atherosclerotic effects, one can assume that this represents a class effect. In concurrence with slowing of the progression of atherosclerosis, ACE inhibitors decrease markers of inflammation and LDL oxidation in the atherosclerotic regions. A variety of AT₁ receptor blockers have also been shown to reduce the progression of atherosclerosis in different animal models. The effects are particularly evident at high doses of AT₁ receptor blockers, which suggests that either high doses block AT₁ receptors more completely than lower doses, or that high doses reduce atherosclerosis by some nonspecific effect. We recently reported the anti-atherosclerotic effect of losartan (25 mg/kg) in rabbits fed a high-cholesterol diet and showed that losartan therapy suppressed the expression of adhesion molecules as well as NF-κB by activating its regulatory protein IkBα.

To determine the specificity of the role of RAS inhibitors (v. the blood pressure-lowering effect), Leif et al. conducted a study with low doses of fosinopril (5 mg/kg/day) or losartan (5 mg/kg/day) that did not lower blood pressure. Control animals were given either a placebo or a dose of hydralazine which lowered blood pressure. Low-density lipoprotein oxidation, as measured by levels of thiobarbituric acid-reactive substances (TBARS) or by formation of conjugated dienes, was suppressed by low-dose fosinopril, suppressed modestly by losartan and unaffected by the placebo or hydralazine. Atherosclerosis was inhibited by fosinopril and losartan, suggesting that the anti-atherosclerotic effects of RAS inhibitors may be due, at least in part, to direct inhibition of LDL oxidation and other effects of Ang II on the vessel wall. Bavy et al. from our laboratory showed that the ACE inhibitor quinapril decreased intra-arterial thrombus formation, whereas the AT₁ receptor blocker losartan had a minimal effect. The inhibitory effect of ACE inhibitors on the generation of plasminogen activator inhibitor-1 may be relevant in this differential effect of ACE inhibitors and AT₁ receptor blockers. This is especially relevant since thrombosis is intimately involved in atherogenesis.

The role of Ang II in promoting atherosclerotic lesions and aneurysms in apolipoprotein (apo) E-deficient mice has been recently examined by Daugherty et al. These investigators showed that a 1-month infusion of Ang II enhanced the severity of aortic atherosclerotic lesions compared to a placebo. Interestingly, there was extensive formation of abdominal aortic aneurysms in apo E-deficient mice infused with Ang II. Further, the presence of hyperlipidemia was necessary for the development of aneurysms. These observations suggest that increased plasma concentrations of Ang II have profound effects on vascular pathology when combined with hyperlipidemia, and inhibitors of RAS may have a therapeutic benefit, especially in the hyperlipidemic state.

**Endothelial function, RAS and Dyslipidemia**

Endothelial dysfunction in hypercholesterolemic animals has been shown to be improved by ACE inhibitors. Bradykinin antagonists can diminish some of this benefit, suggesting that inhibition of bradykinin breakdown rather than inhibition of Ang II formation may be important in this effect. Recently Mancini et al. showed that treatment of patients with coronary artery disease with quinapril improved coronary vasomotion. Quinapril had greater efficacy in improving endothelial function in patients with LDL-cholesterol >130 mg/dl than in patients with LDL-cholesterol <130 mg/dl.
Acetylcholine stimulates release of the potent vasodilator species NO, which is broken down by ROS. One of the mechanisms responsible for improvement in acetylcholine-mediated vasodilatation may be inhibition of Ang II-sensitive, NADH-dependent, superoxide-producing enzymes, resulting in a reduction of NO inactivation. Warnholtz et al.35,36 showed that AT1 receptor blockade inhibited NADH oxidase activity and simultaneously improved endothelial dysfunction in animals fed a high-cholesterol diet. These findings cannot be attributed to lowering of cholesterol levels because treatment with the AT1 receptor blocker has no effect on total or LDL-cholesterol level.

Interaction between ox-LDL and RAS: Role of Receptors for ox-LDL (LOX-1)

We have recently identified high-affinity lectin-like receptors for ox-LDL (LOX-1) in cultured human coronary artery endothelial cells by reverse transcriptase-polymerase chain reaction (RT-PCR), Western blot, and radioligand binding.37–39 Native LDL does not bind to this receptor. Vascular endothelial cells in culture37 and in vivo39 internalize and degrade ox-LDL through this putative receptor-mediated pathway which does not seem to involve the classic macrophage scavenger receptor. Recent studies show that the cytokine TNF-α and fluid shear stress play a role in the regulation of LOX-1 gene expression. The LOX-1 receptor appears to be a major target for scavenging ox-LDL in the arterial wall. Recent unpublished studies from our laboratory have demonstrated that Ang II upregulates LOX-1 gene expression as well as the uptake of ox-LDL in human coronary artery endothelial cells by activation of the AT1 receptor. The effects of Ang II were blocked by the AT1 receptor blockers losartan and candesartan, but not by the AT2 receptor blocker PD 213319. Angiotensin II and ox-LDL exerted a cumulative injurious effect on cells, measured as lactic dehydrogenase (LDH) release and cell viability. Again, AT1 receptor blockers reduced the cumulative injurious effect of Ang II and ox-LDL. Importantly, the chain-breaking antioxidant α-tocopherol also attenuated the injurious effect of ox-LDL and Ang II, emphasizing the importance of redox-sensitive pathways in the cross-talk.40

The cross-talk between ox-LDL and Ang II is further evident from the work of Chen et al.39 from our laboratory, who showed intense immunostaining for and upregulation of the gene for LOX-1 in the atherosclerotic tissue of rabbits fed a high-cholesterol diet. Losartan therapy not only reduced atherosclerosis, but also blocked the upregulation of LOX-1. Recent unpublished studies from our laboratory show marked upregulation of LOX-1 in concert with apoptosis in human atherosclerotic plaques, particularly in the regions that are prone to rupture. Figure 1 shows the interaction of dyslipidemia and RAS in atherogenesis.

**Fig. 1.** Interaction of dyslipidemia and the renin-angiotensin system (RAS) in the development of atherosclerosis. The amplification of RAS by dyslipidemia in particular oxidized LDL may enhance the growth-promoting effect of Ang II (and possibly other growth factors) and upregulate the expression of AT1 receptor. The pro-oxidant effect of Ang II may stimulate oxidation of LDL, degrade nitric oxide and may be related to its pro-inflammatory properties. Ang II promotes expression of genes for LOX-1 and other scavenger receptors, Ang II: angiotensin II; LDL: low-density lipoprotein; Ox-LDL: oxidized LDL; SRs: scavenger receptors; AT1R: angiotensin type 1 receptors; LOX-1: receptors for oxidized LDL; NO: nitric oxide; O2−: superoxide anion; EC: endothelial cells.

**Dyslipidemia and RAS in Hypertension**

The association of hypertension with hyperlipidemia has been noted in several population studies. The prevalence of hypertension is greater in populations with high cholesterol levels. Dyslipidemia may be another metabolic factor that influences blood pressure. However, these studies used older, less rigorous definitions than are currently recommended. Recently, Lloyd-Jones et al.41 evaluated 4962 subjects from the Framingham Heart Offspring Study and cross-clarified them according to the sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). Data were collected from subjects examined between 1990 and 1995.

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The prevalence of dyslipidemia (defined as total cholesterol >240 mg/dl, HDL-cholesterol <35 mg/dl, or currently receiving lipid-lowering therapy) increases with increasing blood pressure in men and women. On average, over 40% of men and 33% of women with blood pressure ≥145/90 mmHg were also dyslipidemic. These data demonstrate that hypertension and hypercholesterolemia are frequently associated, even when current rigorous definitions are used. These observations also suggest that individuals with hypertension may be more likely to become dyslipidemic over time.

Sung et al.49 examined the blood pressure response to a standardized mental arithmetic test in 37 healthy normotensive subjects with hypercholesterolemia (mean total cholesterol 263 mg/dl) and 33 normotensive subjects with normal cholesterol levels. None of the hypercholesterolemic group was receiving lipid-lowering therapy prior to induction in the study. In the first part of the study, blood pressure response during the arithmetic test was determined and found to be significantly higher in the hypercholesterolemic group compared with the normocholesterolemic group (18 v. 10 mmHg, respectively, p=0.005). In the second part of the test, the hypercholesterolemic group was divided into two subgroups which received either 6 weeks of lovastatin or 6 weeks of placebo in a double-blind, cross-over design. There were 26 evaluable patients in this part of the study. Statin treatment resulted in significant reduction from baseline in total and LDL-cholesterol levels and was associated with lower mean systolic blood pressure prior to (119±11 v. 122±9 mmHg, p=0.07) and during the arithmetic test (133±12 v. 141±10 mmHg, p<0.05). Diastolic blood pressure changes were not significantly correlated with lowering of lipid levels. These observations demonstrate that individuals with hypercholesterolemia have an exaggerated systolic blood pressure response to mental stress and the lowering of lipid levels improves the systolic response to stress. Although the effects of elevated cholesterol levels on atherosclerosis are well documented, the modest change in the degree of stenosis demonstrated by angiographic studies is not sufficient to explain the benefit of reduction in cholesterol levels. It may well be that lowering cholesterol levels alters the activity of some neurohumoral mediators such as Ang II and improves vascular tone.

Nazzaro et al.49 also measured post-ischemic forearm blood flow and minimal vascular resistance to evaluate the effects of mental stress on vasodilatative capacity and vascular structure, respectively. These parameters demonstrated the same trends as blood pressure. Both monotherapies improved these parameters, but the combination therapy was associated with a greater improvement than either monotherapy. These findings suggest a close interplay of RAS and lipid metabolism.

Table 1. Common effects of dyslipidemia and RAS in atherosclerosis.

| 1. Both stimulate formation and release of ROS | 4. Both are pro-inflammatory (cause expression of adhesion molecules and cytokines, upregulate the gene for monocyte chemoattractant protein-1 and induce monocyte adhesion) |
| 2. Both cause apoptosis | 5. Both degrade or decrease endothelial nitric oxide synthase (eNOS) expression and hence decrease endothelium-dependent vasodilatation. |
| 3. Both cause activation of redox-sensitive transcription factor NF-κB |

Clinical Benefit of Modulation of RAS and Dyslipidemia in Coronary Artery Disease (CAD)

Although numerous epidemiological studies have shown that elevated levels of LDL are associated with the onset of hypertension and atherosclerosis,50 the underlying mechanisms remain unclear. Angiotensin-converting enzyme inhibition has been shown to promote regression and even prevent atherosclerosis, suggesting a link between atherosclerosis and RAS.51 The clinical benefits from simultaneous modulation of RAS and dyslipidemia are summarized in Table 2. Indirect evidence for an interaction between dyslipidemia and RAS comes from some clinical studies such as Evaluation of Losartan In the Elderly (ELITE)52 and Lipoprotein and Coronary Atherosclerosis Study (LCAS).53 There are studies...
which suggest that RAS may affect responses to lipid-lowering agents. Observations from unpublished data from studies such as the ELITE trial support the hypothesis that combination treatment with ACE inhibitors and statins may have incremental benefit in reducing mortality.

The LCAS was conducted in 429 patients with CAD and at least 1 lesion with ≥30%–75% diameter stenosis. Subjects were randomized to statin (fluvasatin) or placebo for 2.5 years and the primary end-point was a change in the minimum lumen diameter as assessed by quantitative coronary angiography. Marian et al.33 studied the response to statin therapy according to ACE insertion/deletion (I/D) genotype in the LCAS population. The subjects with DD, ID, or II genotypes achieved reductions of 31%, 25%, and 21%, respectively. There was a significant genotype-by-treatment interaction (p=0.005). A similar result was obtained for reduction in total cholesterol. Subjects with the DD genotype also had a higher rate of regression and a lower rate of progression than subjects with the other 2 genotypes.

The effect of ACE inhibition on CAD progression was the subject of the Quinapril Ischemic Events Trial (QUIET). This study showed that quinapril had only a slight effect on the progression of CAD.44 However, in patients with LDL-cholesterol levels >130 mg/dl, there was significantly less progression in the quinapril group. Thus, the rapid progression of disease seen in patients given a placebo with higher LDL-cholesterol levels did not occur in patients treated with quinapril. As in the TRENDS study,45 ACE inhibitors appeared to have greater efficacy in patients with higher LDL-cholesterol levels.

Angiotensin-converting enzyme inhibitors are beneficial in a variety of clinical situations, such as hypertension, diabetes and congestive heart failure. Recent long-term studies with ACE inhibitors in patients with decreased left ventricular function47–49 have shown a decrease in cardiac ischemic events and/or a need for revascularization. One pathogenic factor common to both heart failure and ischemic heart disease is endothelial damage or activation, which may explain the reduction in ischemic events seen in these trials. More so, other clinical studies such as the Heart Outcomes Prevention Evaluation (HOPE) trial50 have further confirmed the benefit of reducing vascular events and death even in patients with normal ventricular function and normal blood pressure with pre-existing vascular or coronary disease. The study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE) trial, a substudy of the HOPE trial, demonstrated the beneficial effect of ramipril in preventing progression of carotid atherosclerosis.51 Similarly, irbesartan, an AT1 receptor blocker, has been shown to regulate markers of inflammation in patients with premature atherosclerosis; this may retarde the inflammatory process seen in atherosclerosis.52 These findings suggest the potential role of RAS in the development and progression of atherosclerosis.

No large randomized study has yet examined the hypothesis of whether treatment by modulation of RAS with drugs (ACE inhibitors or AT1 blockers) combined with lipid-lowering drugs exerts additive or incremental benefits. The ongoing randomized trial may shed light in this direction.44

Summary

Hypertension and hypercholesterolemia, two major risk factors for atherosclerotic disease, frequently coexist in patients with hypertension and CAD. Data from clinical studies suggest the existence of lipoprotein–neurohormonal interactions that may adversely affect vascular structure and reactivity. Data from preclinical studies suggest that

Table 2. Summary of the results of clinical trials suggesting interaction between RAS and dyslipidemia

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Study objective</th>
<th>Results</th>
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<tbody>
<tr>
<td>TRENDS44</td>
<td>Effects of ACE inhibitor (quinapril) in acetylcholine-induced endothelial response of coronary artery according to LDL-cholesterol level</td>
<td>Quinapril 40 mg/day had greater efficacy in improving endothelial function in the group with LDL-cholesterol &gt;130 mg/dl than in the group with LDL-cholesterol &lt;130 mg/dl. There was a significant interaction (p=0.005). A similar result was obtained for reduction in total cholesterol. Subjects with the DD genotype also had a higher rate of regression and a lower reduction in total cholesterol.</td>
</tr>
<tr>
<td>QUIET45,46</td>
<td>Effect of ACE inhibitor (quinapril) on ischemic events and angiographic progression of coronary disease assessed in patients who underwent percutaneous intervention</td>
<td>Both captopril and losartan decreased crude mortality. Similarly, patients who were on statins had additional –50% reduction in mortality.</td>
</tr>
<tr>
<td>LCAS57</td>
<td>Effect of statin (fluvastatin) on minimal lumen diameter assessed by quantitative coronary angiography according to ACE genotype. LDL reduction according to ACE genotype was analyzed</td>
<td>There was a significant difference in the reduction of LDL-cholesterol according to the ACE genotype. Subjects with DD, ID, or II genotype achieved reductions of 31%, 25%, and 21%, respectively.</td>
</tr>
<tr>
<td>ELITE II52</td>
<td>Effect of captopril and losartan on cardiac events in elderly patients with CHF</td>
<td>Both captopril and losartan decreased crude mortality. Similarly, patients who were on statins had additional –50% reduction in mortality.</td>
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</table>
RAS may be upregulated by abnormal lipids, most likely via production of ox-LDL. On the other hand, activation of RAS leads to release of ROS and transcriptional upregulation of LDL and ox-LDL uptake in macrophages, smooth muscle cells and endothelial cells. These findings extend our understanding of the interplay among risk factors to synergistically increase cardiovascular risk, and of the antiatherosclerotic effects of local ACE inhibition to reduce cardiovascular risk. Trials aimed at modifying RAS along with drugs lowering total- and LDL-cholesterol levels and inhibitors of oxidative modification of LDL-cholesterol will address the clinical relevance of this biological interaction.

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Indian Heart J 2001; 53: S11–S18
Right Atrioventricular Metastasis of Hypernephroma

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A 37-year-old man was admitted to our hospital for evaluation of weight loss and pain in the right lumbar region. Ultrasound of the abdomen, computerized tomography and magnetic resonance imaging showed a large mass over the upper pole of the right kidney with extension of the tumor into the inferior vena cava (IVC) extending up to the right atrium. A large, mobile right atrial mass was seen on transthoracic echocardiography and the subcostal view showed the tumor extending into the right atrium from the IVC and prolapsing into the right ventricle (Fig. 1). There were no obstructive signals across the
tricuspid valve. In view of the young age of the patient and the absence of lymphadenopathy and liver metastasis on imaging, it was decided to subject the patient to right nephrectomy and IVC thrombectomy.

Preoperative transesophageal echocardiography (Figs. 2 and 3) confirmed the findings of transthoracic echocardiography. Intraoperatively, there was a large tumor about 20×20 cm in size with a bosselated surface at the upper pole of the right kidney, adherent to the inferior surface of the liver (Fig. 4). Mobilization of the tumor resulted in generalized oozing from the inferior surface of the liver and the patient developed severe hypotension peroperatively. The retroperitoneal space was packed with sterile towels but we lost the patient in the early postoperative period.

Metastatic tumors in the right atrium as a result of direct invasion and extension up the IVC are rare. We report a case of renal cell carcinoma (RCC) which involves the vena cava, extending up to the right atrium and right ventricle. Renal cell carcinoma, a unique neoplasm because of its propensity to propagate into the renal vein and IVC, may involve the heart in two ways. First, in 5%–10% of cases, the primary tumor invades the IVC and in 10%–40%, it further extends up the vena cava into the right atrium. Second, the primary tumor metastasizes to the heart in 10%–20% of patients, who die of systemic spread of the RCC. Right atrial masses can be benign or malignant, primary or secondary. Echocardiographically, primary tumors commonly originate from the interatrial septum, the most common being the right atrial myxoma. Secondary infiltrative tumors of the heart are by far more common and usually extend into the right atrium from the IVC (and less commonly from the right atrial free wall). Tumor extension along the IVC and into the right atrium is the mechanism of intracardiac tumor spread, most frequently described in RCC, Wilm’s tumor, hepatoma and uterine leiomyoma. One case of a hypernephroma prolapsing through the tricuspid valve, causing tricuspid inflow obstruction and a right-to-left shunt through a patent foramen ovale has also been reported.

Metastatic involvement of the right atrium by an RCC via the IVC is one possible cause of a right atrial mass. Imaging of the IVC (subcostal view) can show the tumor originating from the IVC, thus avoiding confusion with tumors which have a primary origin in the heart.

References
Egg Shell Calcification of the Aorta in Aortoarteritis

The report by Sivakumar et al.\textsuperscript{1} of unusual, extensive, dense and nodular calcification of the aorta in aortoarteritis made interesting reading. In this context, it may be relevant to present a different pattern of calcification in aortoarteritis.

The patient was a 22-year-old woman with type III nonspecific aortoarteritis. A rim of calcification of the aorta extended from the ascending to the abdominal aorta (Fig. 1). No treatment was offered. Egg shell calcification of the aorta is uncommon in young adults. Our case highlights the unusual presentation of the condition. The appearance is so typical that the diagnosis can usually be suspected from a simple chest X-ray.

Fig. 1. Chest X-ray chest in postero-anterior view showing egg shell calcification from the ascending aorta to the abdominal aorta (arrows).

Reference


Pacemaker “Like” Syndrome

An 82-year-old male had a history of long-standing bronchial asthma, hypertension, coronary artery disease (single-vessel disease), and presented with complaints of brief episodes of giddiness with slurring of speech for the past few weeks. He had been admitted two years ago with paroxysmal atrial fibrillation with left ventricular systolic dysfunction and pulmonary edema.

During one of the episodes, a cardiologist noted a normal pulse. Electroencephalogram (EEG) and Holter monitoring during another episode were normal. We noted a normal pulse with exaggerated neck pulsations. Repeat Holter monitoring captured two 30 s long symptomatic episodes of junctional rhythm (isorhythmic atrioventricular (AV) dissociation) (Fig. 1). His medications were modified to suppress automaticity.

Hypotension and neurological symptoms due to cerebral hypoperfusion occurred in the patient due to loss of AV synchrony. A normal pulse during “symptom” is rare in patients with symptomatic arrhythmias except in the pacemaker syndrome. The symptoms of pacemaker

Fig. 1. Sinus rhythm (average; RR 830 ms) and transition to slightly faster junctional rhythm (average; RR 780 ms) (arrow) which lasted for 45 s.

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syndrome include orthostatic hypotension, near syncope, light headedness and disturbed mentation. The mechanism of symptoms in our patient is similar to that seen in the pacemaker syndrome.

References

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Limitation of Computerized Averaging During Stress Test

Use of computerized averaging of an electrocardiogram (ECG) in stress testing has facilitated the removal of motion artifacts and baseline shifts. It also facilitates continuous on-line analysis of ECGs during the test period. This process, however, introduces some errors which are not widely appreciated by clinicians. We report three cases in which computerized averaging of the QRS complex resulted in incorrect interpretation of data. All tests were performed on ECT WS 2000 (Medtronix) machine.

Case 1: A 50-year-old male was subjected to computerized stress testing for chest pain. During step 2, he developed a run of broad QRS tachycardia (Fig. 1A and B).

Computerized averaged beats for that period (Fig. 1a and b), however, revealed a narrow QRS complex. Broad QRS tachycardia was missed when only averaged complexes were analyzed.

Case 2: A 42-year-old male was subjected to computerized stress testing for breathlessness on effort. During hyperventilation he developed isolated unifocal premature ventricular contractions (Fig. 2A and B). The computer selected one such beat and reproduced it as an averaged complex (Fig. 2a and b). When only averaged complexes were analyzed, it was incorrectly interpreted as hyperventilation-induced intraventricular conduction defect.

Case 3: A 57-year-old male was subjected to computerized stress testing for atypical chest pain. His resting ECG revealed a right bundle branch block with a normal QRS axis. During step 4, he developed left posterior hemiblock (Fig. 3A and B). Computer-averaged beats for that period, however, did not show the change in QRS axis (Fig. 3a and b). An analysis of averaged beats alone missed the left posterior hemiblock.

Computerized systems use the following methods:
1. Selecting the best complex (QRS complex with least noise and baseline wander) for analysis and rejecting the rest of the data.
2. Averaging of all morphologically similar, dominant QRS complexes and rejection of beats with a different configuration.

Irrespective of the method used, the computer rejects part of the recording while producing an averaged complex. This rejection process can involve clinically useful information. Averaged beats selected by the computer,
Raw electrocardiogram showing left posterior hemiblock during stress test. Computer-averaged beats not showing the left posterior hemiblock. Therefore, do not always reflect the raw ECG data. It is thus important that a print-out of raw data should be taken during each step of exercise and compared with averaged complexes before making a final decision.

References


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Platelet Glycoprotein IIb/IIIa Inhibition with Coronary Stenting for Acute Myocardial Infarction (ADIRAL Trial)

Summary
This multicenter, double-blinded trial involving 300 patients with acute myocardial infarction (AMI) studied the efficacy of glycoprotein (Gp) IIb/IIIa inhibitor (abciximab) given before primary stenting. Inclusion criteria were broad and comprised patients who had the first symptoms of AMI within 12 hours before enrollment. All the patients received aspirin and were randomized to receive either abciximab or a placebo as soon as possible (in a mobile ICU, the casualty department, in the ICCU or in the catheterization laboratory), in all cases before sheath insertion and coronary angiography (CART). Patients received either abciximab as a bolus of 0.25 mg/kg, followed by a 12-hour infusion at a rate of 0.125 µg/kg/min or a matched placebo. Heparin was given as an initial bolus of 70 U/kg (maximum 7000 U) with additional doses given as necessary to maintain an ACT of 200 s. After coronary angioplasty (PTCA), a continuous infusion of heparin 7 U/kg/hour was initiated and maintained till check angiography was obtained 24 hours after the procedure. Sheaths were removed 4–6 hours after the check angiography and ticlopidine administered till 30 days after the procedure. A stent was implanted if the diameter of the infarct-related artery (IRA) was greater than 2.5 mm with no unsuitable anatomic features. The primary end-point was a composite of death, reinfarction or urgent target vessel revascularization (TVR) at 30 days. It was significantly reduced in the abciximab group (6%) compared to the placebo group (14.6%, p=0.01). At 6 months also, it was significantly reduced in the abciximab group (7.4% v. 15.9%, p=0.02). The superior response in the abciximab group could perhaps be attributed to greater TIMI grade 3 flow before the procedure (16.8% v. 5.4%, p=0.01), immediately afterwards (95.1% v. 86.7%, p=0.04), and 6 months later (94.3% v. 82.8%, p=0.04). The primary end-point at 30 days had occurred in only 7.4% of patients with TIMI grade 3 flow at the end of the procedure as compared with 35.3% of the patients with TIMI grade 0, 1 or 2 flow (p<0.001). This difference persisted at 6 months (p=0.001). Minor bleeding was higher in the abciximab group (12.1% v. 3.3%, p=0.04) and there was 1 major bleed in this group versus none in the placebo group. The authors concluded that as compared with placebo, early administration of abciximab before stenting improves coronary patency and clinical outcomes and the response persists for at least 6 months.

Comments
The superiority of a strategy of primary angioplasty with stenting over conventional thrombolysis in patients presenting with AMI has now been well established. In a recent study, LeMay et al. have shown that while a strategy of primary stenting was clearly superior to that of accelerated t-PA in terms of the composite end-point of death, reinfarction, stroke or repeated TVR at 6 months (24.2% v. 55.7%, p<0.001), mortality was actually higher in the primary stenting group, (4.8% v. 3.3%) (though statistically not significant). One possible reason could be a high thrombus load. In their study, the routine use of abciximab was discouraged. It is logical to assume that the effects of abciximab and stenting will be complementary. At present, data on the use of abciximab in patients undergoing primary angioplasty and stenting are limited. In the present study, abciximab in combination with stent placement reduced both the incidence of acute ischemic events and subacute events related to clinical restenosis. The beneficial effect of this combination accrues probably from better procedural success, better patency of the IRA, reduced rate of reocclusion, and better left ventricular function at follow-up. Left ventricular functioning may also have been better preserved due to other beneficial mechanisms attributable to abciximab, i.e. less distal embolism, less side-branch closure and improvement in microcirculation. The benefits of abciximab were also demonstrated in the high-risk subgroup of patients with diabetes, small coronary arteries or cardiogenic shock. However, an inordinately high rate of bleeding complications is a cause of concern. In contrast to the prevailing practice of using low-dose heparin, in the present study, a higher dose of heparin was given (with excessively high ACT, mean of 316, and APT, mean of 2.2, in the abciximab group). Furthermore, a prolonged infusion of heparin was given and the sheaths were removed more than 24 hours after the procedure. Although the characteristics of the patients enrolled in the two groups appear to be matched overall, there were more diabetics, hypertensives and patients with CHF in the placebo group and, therefore, some bias may have crept into the results.
Effects of Pretreatment with Clopidogrel and Aspirin Followed by Long-Term Therapy in Patients Undergoing Percutaneous Coronary Intervention: The PCI-CURE Study


Summary
This was a prospectively designed study of 2658 patients who underwent percutaneous coronary interventions (PCI) in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial and were randomly assigned to double-blind treatment with clopidogrel (n=1313) or placebo (n=1345). The aim was to test the efficacy of treatment with clopidogrel in addition to aspirin prior to performing PCI in preventing major ischemic events afterwards and determine the possible benefits of its long-term use following PCI in patients with non-ST segment elevation acute coronary syndromes (ACS). Inclusion criteria were: patients presenting with symptoms indicative of ACS within the last 24 hours in the absence of >1 mm ST segment elevation on the electrocardiogram (ECG), but with ECG evidence of new ischemia, or cardiac enzymes or troponin levels at least twice the upper limit of normal. Exclusion criteria were: standard contraindications for antithrombin drugs, NYHA class IV, previous coronary artery bypass grafting (CABG), PCI within 3 months or use of glycoprotein (Gp) IIb/IIIa inhibitors within the last 3 days. Clopidogrel or a matching placebo was started in addition to aspirin after randomization till the time of PCI, following which open-label thienopyridine (clopidogrel or ticlopidine) was given for 2–4 weeks. After this, clopidogrel or placebo was continued for the next 3–12 months. The primary end-point was a composite of cardiovascular (CV) death, myocardial infarction (MI) or urgent target vessel revascularization (TVR) within 30 days of PCI. Significantly fewer patients developed MI on clopidogrel prior to PCI (3.6% vs 5.5%, p=0.04). On follow-up at 30 days after PCI, there was a significant reduction in the primary end-point in the clopidogrel group (4.5% vs 6.4%, p=0.03). The composite of cardiac death or MI was also lower (2.4% vs 4.4%, p=0.04), mainly because of a significant reduction in all MIs (2.4% vs 3.8%). After excluding nearly 25% of patients who received open-label thienopyridine prior to PCI, the 42% reduction in the primary end-point was still highly significant in the clopidogrel group (4.2% vs 7.2%, p=0.005). This benefit occurred regardless of the use of stents (6.1% vs 3.5%, p=0.016). There was a nonsignificant but consistent reduction in the rate of CV death or MI (3.1% vs 3.9%) from 30 days to 8 months post-procedure. However, the composite reduction in CV death, MI or rehospitalization (25.3% vs 28.9%) reached significance during this period. Overall (including events before or after PCI), there was a 31% reduction in CV death or MI. Taken separately, there was a significant reduction in the primary end-point in the period before PCI, from PCI to 30 days post-procedure and from PCI to the end of follow-up. The lower rate of primary end-points was seen as early as 2 days after PCI, indicating that the early benefit was mainly due to the effects of pre-treatment with clopidogrel. There was no significant difference in the complications, including major bleeding, though there was an excess of minor bleeding episodes (3.5% vs 2.1%, p=0.03) in the clopidogrel group.

Comments
This study has shown for the first time the long-term incremental benefit of using another antiplatelet agent along with aspirin in the reduction of death or MI, both before and after PCI for ACS. The significant benefit seen in the clopidogrel group even during the 30 days after PCI, when all the patients received open-label thienopyridine, shows that the average pre-procedure 6-day therapy with clopidogrel also had a significant benefit in terms of preventing platelet thrombus-mediated events. The impact was seen as early as 48 hours after PCI and increased over 7 and 14 days, even though there may be some masking of benefit due to the use of open-label thienopyridine in about 25% of patients pre-PCI in both groups. This benefit is maximum for reduction in MI, especially Q-wave MIs. The 32% reduction in death or MI in the period prior to PCI strongly supports the use of this drug electively in patients with ACS in whom an invasive strategy is being considered. The continued benefit of the use of additional clopidogrel over 8 months of follow-up was due to the reduction in the risk of rupture of the atherosclerotic plaques in areas other than the culprit lesion site. Moreover, long-term additional clopidogrel use may prevent late stent occlusion in some cases as neointimal and endothelial coverage of the stent requires 3–6 months. All these benefits are accompanied by an increase in minor but not major or life-threatening bleeding events. The only issue is the cost of this new drug, which continues to be high and beyond the reach of a vast majority of our population, especially if long-term use is advocated.
Reperfusion Therapy for Acute Myocardial Infarction with Fibrinolytic Therapy or Combination Reduced Fibrinolytic Therapy and Platelet Glycoprotein IIb/IIIa Inhibition: The GUSTO Randomized Trial

Summary
The GUSTO V study was a randomized open-label trial which compared the efficacy of reteplase alone with reteplase plus abciximab in patients with acute myocardial infarction (AMI). Overall, 16,588 patients with evolving ST segment elevation AMI presenting within 6 hours of onset of chest pain were randomized to receive either full-dose reteplase (two 10 U boluses, 30 min apart), or a combination of half-dose reteplase (two boluses of 5 U, 30 min apart) plus a standard abciximab dose. All the patients were given aspirin and heparin; however, the dose of heparin was reduced in the group given the combination.

The primary end-point was 30-day mortality and secondary end-points included the various complications of AMI. All the baseline characteristics, including the use of adjunctive drugs, were matched in the two groups. However, the time of initiation of thrombolysis was earlier in the reteplase arm (1.6 vs. 2.2 hours in the combination arm). Although 30-day mortality was lower in the combination group (5.6% vs. 5.9%), it was not statistically significant (p=0.43; 95% CI: 0.83–1.08). However, the composite of death and nonfatal MI was lower (7.4% vs. 8.8%, p=0.001) in the combination group and there was a lesser need for urgent percutaneous coronary intervention (PCI) and fewer major nonfatal ischemic complications of AMI with the combination than reteplase alone. The rate of spontaneous hemorrhage, predominantly from gastrointestinal sources, was significantly higher in the combination group (4.6% vs. 2.3%, p<0.0001). Except in the elderly (>75%), the risk of intracranial hemorrhage was not different (1% vs. 0.9%, p=0.55). The authors conclude that although the combination of low-dose reteplase and abciximab was not superior to reteplase alone as per 30-day mortality, there was a consistent reduction in complications of AMI, such as reinfarction or need for urgent PCI or CABG. The beneficial effects of the combination therapy were countered balanced to some extent by an increase in nonintracranial bleeding.

Comments
Since their initiation in 1990, the GUSTO series of studies have broadened our understanding of the pathophysiology of AMI and have made an impact on prevailing clinical practice. The present study, GUSTO V addresses the limitations of fibrinolytic therapy alone and investigates the efficacy of a combination of fibrinolytic therapy with potent antithrombin agents in reducing the hard end-point of 30-day mortality. The limitations of fibrinolytic therapy alone (delayed and incomplete restoration of TIMI grade 3 flow, reocclusion of opened artery and lack of tissue reperfusion) are well recognized. One of the strategies to overcome this problem is to perform primary angioplasty. However, because of limited accessibility and the high cost involved, primary PTCA may not be a viable option in the vast majority of patients. One of the mechanisms limiting effective tissue perfusion in thrombolysis has been microembolization of platelet-rich clots and the paradoxical prothrombotic effect of fibrin degradation products (arising from fibrinolysis). Aspirin, as such, is only a mild antithrombin agent. In this context, potent antithrombotic agents such as glycoprotein IIb/IIIa receptor antagonists may hold a key to this problem. Several phase II trials evaluating a combination of these two agents have provided the pathophysiological basis of this hypothesis. The TIMI 14 trial enrolled 888 patients of AMI and randomized them to receive either accelerated t-PA, abciximab bolus plus infusion, or a combination of abciximab with reduced doses of t-PA or STK. A prompt and significant increase in the rate of TIMI grade 3 flow at 90 min in the combination group of low dose t-PA with abciximab was demonstrated and this improvement occurred without an increase in the risk of major bleeding. Similarly, other studies, such as SPEED and INTRO-AMI, also showed the beneficial effects of this combination. However, none of these phase II trials were powered to investigate mortality reduction. In contrast, GUSTO V is a megatrial involving >16,000 patients. In this study too, although there was a significant reduction in all of the nonfatal complications of AMI, the primary end-point of mortality reduction was not affected. There could be several reasons for this. Perhaps, due to better management of AMI (in both the groups), mortality itself is low; therefore, a still larger number of subjects may be required to achieve a significant difference in mortality. Secondly, 30-day mortality may not be the right time-frame for this parameter. The benefits accrued by this combination are likely to manifest over a longer period of time, perhaps 1 year. Finally, thrombolysis was achieved earlier in the reteplase group (1.6 v. 2.2 hours in the combination group) perhaps due to technical reasons and this may counterbalance the beneficial effect of the combination. The open-label design of the study is a technical, though unavoidable, flaw in the trial.
Randomized, Placebo-Controlled Study for Immunosuppressive Treatment of Inflammatory Dilated Cardiomyopathy


Summary

This study was a randomized, placebo-controlled trial comparing the short-term efficacy of immunosuppressive therapy (prednisone and azathioprine) with a placebo in patients with idiopathic dilated cardiomyopathy (IDC). Eighty-four patients of chronic heart failure (>6 months) with an ejection fraction ≤40% and increased expression of human leucocyte antigen (HLA) on endomyocardial biopsy (EMB) specimens were included in the present study. Patients suspected of having coronary artery disease (CAD) based on the clinical findings or having two or more risk factors underwent coronary angiography to rule it out and those with more than 50% coronary artery stenosis were excluded from the present study. On the basis of the Dallas criteria, 7 patients (8.3%) had active myocarditis, 16 (19%) had borderline myocarditis and 61 (72.6%) had no myocarditis. All the patients received conventional therapy, including diuretics, β-blockers, and angiotensin-converting enzyme (ACE) inhibitor and β-blockers. These immunohistologically verified chronic myocarditis patients were then randomized to placebo or immunosuppressive therapy with steroids and azathioprine. Prednisone was started at a dose of 1 mg/kg/day initially and then tapered to a maintenance dose of 0.2 mg/kg/day for a total of 90 days. Azathioprine was given at a dose of 1 mg/kg/day for 100 days. The patients were followed up over 2 years. The primary end-point was a composite of death, heart transplantation and hospital re-admission. At the end of 2 years, there was no difference in the composite end-point in the immunosuppressive therapy group (22.8%) compared with the placebo group (20.5%). Left ventricular ejection fraction (LVEF) increased significantly both at 3 months and at the end of 2 years in the immunosuppressive group. Furthermore, protocol-specified definition of improvement was significantly higher in the immunosuppressive group, both at the end of 3 months (71.8% vs. 20.9%, p<0.001) and at the end of 2 years (71.4% vs. 30.8, p<0.001).

Comments

Inflammatory dilated cardiomyopathy is a heterogenous disease. The diagnosis may be based on clinical, histopathological or immunohistological criteria. While conventional therapies like diuretics, ACE inhibitors and β-blockers provide symptomatic benefit and retard the progression of the disease, they are not really helpful in reversal of the disease process. As cardiomyopathy is an immunological disorder, immunosuppressive therapy seems logical if ongoing inflammation is detectable by immunohistochemistry. In practice, however, the usage has been controversial. While some investigators, like Parrillo et al. and Mason et al., have failed to show any benefit with immunosuppressives, others like Maisch and Shulthess have shown the benefit of this type of therapy. The difference in the results can probably be explained by the difference in the diagnostic criteria utilized for the inclusion of patients in these studies. Parrillo et al. utilized clinical criteria for diagnosis and included 102 patients. Patients receiving prednisone showed no overall improvement in the clinical criteria and LVEF. Mason et al. randomized 111 patients by histological Dallas criteria (lymphocyte infiltration and myocarditis) and acute myocarditis. At the end of 12 months, both immunosuppressive and control groups showed an equivalent improvement in EF. However, there were several limitations of these studies: (i) histological features of myocarditis (unlike immunohistological features) tend to be focal and therefore can be missed in EMB; (ii) clinical features were not very specific; active myocarditis was detected in only 8% of patients enrolled on the basis of clinical criteria; (iii) there was widespread disagreement on the same biopsy specimen among different pathologists (when the Dallas criteria were used) to the tune of 40%; (iv) as many as 30% of patients were lost to follow-up. In this context, immunohistological techniques are not only more sensitive but also more specific. In the present study, upregulation of human leucocyte antigen (HLA) has been used as a diagnostic criterion. Identification of HLA proteins on the surface of cells has been correlated with autoimmune reactions and is invariable in inflammatory IDC. This criterion may represent an advancement in diagnostic techniques based on the better understanding of the pathogenesis of IDC and its application in clinical management. In the present study, although the primary end-point was not different at the end of 2 years, patients on immunosuppressive therapy demonstrated an impressive increase in LVEF at 3 months and 2 years. However, there are some limitations of the present study. The criterion of HLA upregulation requires validation in a larger study. Patients with acute heart failure (<6 months) were excluded. The authors reasoned that CHF in a large proportion of these patients would anyway be reversible. The study had a high drop-out rate (31%). Finally, the study could not be truly blinded as steroid therapy is identifiable clinically by cushingoid features.
Calendar of Conferences

November 11–14, 2001, 74th Scientific Session, American Heart Association, Anaheim, California, USA
Contact: American Heart Association, 7320, Greenville Avenue, Dallas, Texas 75231, USA
Fax: 1 214 373 3406

December 6–9, 2001, 53rd Annual Conference of Cardiological Society of India, Hyderabad, India
Contact: Professor P Krishnam Raju, Organizing Secretary, Care Hospital, D. No. 6-3-248/1, Former Hotel Bhaskara Palace, Road No. 1, Banjara Hills, Hyderabad 34
Fax: 040-6668888
e-mail: drkrishnamraju@hotmail.com

January 4–6, 2002, 5th Annual NewEra Cardiac Care 2002: Innovation & Technology, California, USA
Contact: Dr W Randolph Chitwood, 1835, South Center City Parkway, PMB 513 Escondido, CA 92025, USA
Fax: 1 760 839 1250

February 1–3, 2002, Annual Conference of International Society for Heart Research – Indian Section, Thiruvananthapuram, India
Contact: Professor CC Kartha, Division of Cellular & Molecular Cardiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram
Fax: 91-471-446433/550728
e-mail: cckartha@sctimst.ker.nic.in

February 8–10, 2002, Vlth World Congress of Echocardiography and Vascular Ultrasound, New Delhi, India
Contact: Dr (Col) SK Parashar, Secretary General, C-144, Sarita Vihar, New Delhi 110044
Fax: 6942222
e-mail: parashar@del6.vsnl.net.in

March 17–20, 2002, 51st Annual Scientific Sessions, American College of Cardiology, Atlanta, Georgia, USA
Contact: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814, USA
Fax: 1 301 897 9745

May 5–9, 2002, XIV World Congress of Cardiology, Sydney, Australia
Contact: The Congress Secretariat, QVB Post Office Locked Bag Q4002, Sydney, NSW 1230, Australia
Fax: 61 2 9290 2444
e-mail: wcc@icms.com.au

June 8–11, 2002, Heart Failure Update 2002 – From Damage to Defence, Oslo, Norway
Contact: European Society of Cardiology, The European Heart House, 2035 Route des Colles, LesTempliers – BP 179, Sophia Antipolis Cedex 06903, France
Fax: 33 4 9294 7601
e-mail: webmaster@escardio.org

June 19–22, 2002, A World Congress in Cardiac Electrophysiology, Nice, France
Contact: Dr Jacques Mugica, Cardiostim 12 rue Pasteur, Saint-Cloud 92210, France
Fax: 33 1 4602 0509
e-mail: cardiostim@wanadoo.fr

July 17–21, 2002, 14th Asean Congress of Cardiology, Kuala Lumpur, Malaysia
Contact: Dr David KL Quek, Chairman, Organizing Committee, c/o Letter Box 1502, 15th Floor, Menara Meris, 1 Jalan 19/3 Petaling Jaya 46300, Selangor, Malaysia
Fax: 60 3757 8363

August 31–September 4, 2002, XXIV Congress of the European Society of Cardiology, Berlin, Germany
Contact: European Society of Cardiology (ECOR), B.P. 174, Sophia Antipolis Cedex F-06903, France
Fax: 33 49244 7601

Contact: The Course Directors, 55 East 59th Street, 6th Floor, New York, NY 10022–1112, USA
Fax: 212 434 6386
e-mail: info@crf.org

November 17–20, 2002, 75th Annual Session, American Heart Association, Chicago, Illinois, USA
Contact: American Heart Association, 7320 Greenville Avenue, Dallas, TX 75231, USA
Fax: 1 214 373 3406