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INSIDE

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LVAD Platform for Long-Term Drug Therapy in Severe CHF

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Source: Birks EJ, et al. Left Ventricular Assist Device and Drug Therapy for the Reversal of Heart Failure. *N Eng J Med*. 2006;355:1873-1884.

STAGE D OR CLASS IV CONGESTIVE HEART FAILURE (CHF) IS AN ominous clinical state associated with high mortality. Recent advances in pharmacotherapy and resynchronization therapy have been widely publicized, but destination therapy with left ventricular assist devices are unfamiliar to many cardiologists. This is a report from Harefield Hospital in the United Kingdom describing a group of 15 patients with severe CHF and marked depression of left ventricular systolic function, who were treated with a 2-stage therapeutic intervention consisting of a left ventricular assist device (LVAD) and standard CHF medical therapy, followed by treatment with clenbuterol (clen), a highly selective b2 blocker. After a mean of 10 months, 11 of the 15 patients were able to undergo explantation of the LVAD. One cardiac and one non-cardiac death occurred after explantation. Freedom from recurrent heart failure in the survivors was 100% at one year and 89% at 4 years. Multiple parameters, including echocardiography, cardiac catheterization, exercise, and the use of the Minnesota Living with Heart Failure questionnaire, confirmed marked improvement in the survivors, with a significant reduction in left ventricular size and improvement in left ventricular ejection fraction (EF) into the normal range. All hemodynamic parameters, including mean maximal oxygen uptake, were markedly better after explantation than at the implantation of LVAD treatment. This remarkable report supports the concept that "prolonged, near complete unloading of left ventricle with the use of an LVAD. . . . may be associated with structural reverse remodeling. . .and functional improvement." Of note, other research in this field has produced disappointing results, with only 5–24% of individuals able to

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undergo explantation and a high incidence of early recurrence of CHF.

The protocol consisted of the use of a Thoratec HeartMate LVAD in combination with drugs known to produce reverse LV remodeling, followed by a β_2 agonist clenbuterol, which is not available in the United States. All patients had non-ischemic cardiomyopathy and no evidence of acute myocarditis on biopsy. All had class 4 or stage D heart failure, unresponsive to intensive medical therapy. Efforts to enhance reverse remodeling included an ACE inhibitor, an ARB, carvedilol, and spironolactone. After maximal regression of LV systolic and diastolic diameters with the LVAD in place (constant LV size for at least 2 weeks), clen was added to the medical regimen. Carvedilol was replaced by bisoprolol, a selective β_1 blocker.

A variety of monitoring approaches were utilized, including repeated echocardiography with quantitative cardiac measurements, a 6-minute walking test in individuals who were able to go off the LVAD for 20 minutes, and subsequently a 450 meter 6-minute walk. Cardiac catheterization was performed before LVAD implantation, before clen, and before explantation. To be eligible for explantation, patients had to have an LVEDD of < 60 mm, an LVSD of < 50 mm, and LVEF of > 45%. In addition, LVEDP or pulmonary wedge pressure needed to be normal and relatively normal oxygen consumption with exercise was required. After explantation, patients underwent an echo, cardiopulmonary exercise, and repeat cardiac catheterization at 3 months and one year.

Quality of life was assessed 3 years after explantation. The initiation of the LVAD therapy occurred over a 7-month period, beginning in December of 1999. After excluding ischemic cardiomyopathy and other significant co-morbidities, a total of 15 patients were enrolled to receive the combination therapy. Myocardial histology at the time of LVAD implantation demonstrated interstitial and replacement fibrosis and myocyte hypertrophy, compatible with a dilated cardiomyopathy. Eleven of the 15 patients who completed the phase one combination therapy met LVAD explantation criteria. Mean duration of LVAD support was 320 ± 186 days. Two patients underwent cardiac transplantation after completing the full course of combination therapy. Actuarial survival rate at one and 4 years after explantation was 91% and 82%, respectively.

Minimal follow-up after explantation was 4 years on average; all survivors were in NYHA class-1, except for one person who deteriorated after excessive alcohol intake. Thus, among the survivors, the cumulative rate of freedom from recurrent CHF at 1 and 4 years was 100% and 89% respectively. Follow-up at a mean of 5 years demonstrated a mean LVEF of 64% ± 12%, an LVEDD of 59mm, an LVSD of 42.5 mm ± 13 mm, VO_2 of 26 ml/kg/min. Hemodynamics by cardiac catheterization at 3 months and one year after LVAD explantation were essentially within the normal range, except for mildly depressed cardiac index.

The authors conclude that severe CHF "can be reversed in selected patients without acute myocarditis with the use of a specific sequence of mechanical and pharmacologic therapy." Hemodynamic and clinical improvement to relatively normal levels occurred in all patients who were able to complete the dual therapy, and were maintained for more than 4 years in most. Thus, 75% of the 15 individuals who received the full course of combination therapy recovered, and 46% of all patients in the study had a complete recovery. The "rate and duration of recovery. . . were significantly higher than previously reported after LVAD implantation." The authors comment that the initial phase of therapy was to reverse LV remodeling, and the second phase, not as well established, was to utilize selective β_2 stimulation, for which there is positive experimental work in animals and patients. It is suggested that clen treatment may prevent some of the adverse myocyte atrophy seen in long-term mechanical unloading of the heart.

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VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Gerard Gernazian.

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Few side effects were noted, other than mild tremor and muscle cramps in phase-2. The authors asserted that "sustained reversal of severe heart failure secondary to non-ischemic cardiomyopathy could be achieved in selected patients." They call for further studies to assess the reproducibility and durability of these findings.

An accompanying commentary (Renlunde DG, Kfoury AG. *N Engl J Med.* 2006;355:1922–1924) was supportive of this approach, while raising some questions about the study protocol. Specifically, they ask whether both a first and second phase choice of pharmacotherapy was necessary; they also question whether the patients all had severe or stage D heart failure. They stress the careful selection of the patients and point out that not all patients had a good response. Nevertheless, they conclude that there is a "preponderance of evidence supporting these results." They conclude that stage D heart failure treatment now includes not only transplantation or permanent LVAD implantation, but the possibility of prolonged LVAD use, with robust pharmacologic support, followed by careful explantation in patients who improve.

COMMENTARY

The increasing sophistication and number of heart failure programs around the United States have changed the nature of treatment for severe heart failure, with more aggressive LVAD utilization as well as enhanced standard pharmacologic support. This report of a study initiated 5–6 years ago, is an exciting preliminary description of the use of an LVAD as a "platform" for pharmacologic therapy, followed by removal of the device if clinical and hemodynamic parameters are concordant with considerable reversal of remodeling, ie, diminution of LV cavity size, improvement in systolic function to within the normal range, and increases in clinical and exercise status. Clearly, the sophistication of the heart failure center needs to be great. This study was headed by a surgeon, Dr. Magdi Yacoub. It should be noted that the RAAS system was attacked both by an ACEI and an ARB, and, in addition, an aldosterone blocker. Thus, the regimen included the greatest degree of interference with the RAAS system available. Whether ACEI and ARB together were useful in improving the outcomes is difficult to assess. This report, while representing only a small number of individuals who received up-to-date approaches to the failing heart, should stimulate workers in the field to continue innovative basic and clinical research for class D patients. ■

Statins for Heart Failure

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Synopsis: *Among adults diagnosed with heart failure who had no prior statin use, incident statin use was independently associated with lower risks of death and hospitalization among patients with or without coronary heart disease.*

Source: Go AS, et al. Statin Therapy and Risks for Death and Hospitalization in Chronic Heart Failure. *JAMA*. 2006;296:2105–2111.

YET ANOTHER OBSERVATIONAL STUDY HAS BEEN PUBlished that strongly suggests the value of concomitant statin treatment in a medical condition that is not clearly related to dyslipidemia. Because of prior reports in the literature regarding the favorable effect of statin utilization in patients with heart failure (in non-randomized or prospective trials), Go and colleagues from the Kaiser Permanente of Northern California Group, initiated an elaborate observational protocol in an attempt to identify whether statin treatment in patients with congestive heart failure is or is not beneficial. The medical records of almost 10,000 patients were carefully reviewed and a wide variety of potential confounding factors, ie, drug therapy, socio-economic status, were collected. The study only utilized data regarding the incidence in statin use in patients who were not receiving a statin at the study entry date, and who were eligible for treatment based on the national guidelines. The authors controlled for a wide variety of medications used in the treatment of heart failure; data on race and ethnicity were included. Renal dysfunction and multiple other diagnoses were assessed using ICD-9 codes, laboratory data, etc. Left ventricular function was obtained from health plan databases. Reduced left ventricular systolic function was defined as of an LV ejection fraction of < 40% or a designation of moderate or severely reduced systolic function; preserved LV function was defined by an LVEF of > 40% or a qualitative statement of "only mildly reduced systolic function." Enrollment in the database could occur at any time during the 9 year window. A wide variety of statistical techniques were utilized, and many baseline demographic characteristics were identified.

Twenty-five thousand adults with CHF and no prior

statin use were identified and considered eligible for lipid-lowering therapy. During follow-up, half of these individuals initiated statin therapy; these patients tended to be younger and male, but no other clinical differences were noted. There was a higher prevalence of coronary heart disease (CHD), diabetes, and hypertension in those individuals initiating statin therapy during the observational period. Baseline use of multiple drugs used for heart failure therapy and other lipid-lowering drugs were also higher among patients who initiated therapy during the study period.

Results: Median follow-up was 2.4 years, during which time 8,200 patients died and 9,200 patients were hospitalized for CHF. Age- and gender-adjusted rate of death was substantially lower in the statin therapy group, 14.5 per 100 person years vs 25.3 per 100 person years. Known CHD did not affect the data. Rates of hospitalization for heart failure were lower in those who began statin therapy vs those who did not, 21.9 per 100 person years vs 31.1 per 100 person years, $P < 0.001$. In the primary analysis (intention to treat analysis), incident statin use was associated with a 24% lower relative risk of death compared to patients not taking a statin, even after adjustment for multiple co-morbidities, socio-economic factors, etc. In a secondary, time-dependant, exposure analysis, the risk of death was even greater than in the primary analysis, with a hazard ratio of 0.66. Hospitalizations for CHF were 21% lower using the intent-to-treat approach.

The authors comment on theoretical benefits as well as adverse effects of statins. Two studies are cited that come to the same conclusion. However, "the present study attempts to overcome many. . .methodological challenges" that are related to the wide variability of data collection in other reports. The authors emphasize that the Kaiser population was "large and socio-demographically diverse," including patients diagnosed with CHF in and out of the hospital. Efforts were made to improve the power of this observational study. "Overall, statin therapy remained a robust predictor of improved outcomes." The authors stress that they could not exclude residual confounding or selection bias, despite a wide number of adjustments for many population characteristics. They note that limited other experimental data are available, and that randomized trials have utilized relatively small sample sizes and had mixed results. They point out that several very large prospective randomized trials will be available in the future to resolve this issue and to "clarify the role of statins in the management of heart failure."

COMMENTARY

This study fits in with many reports in a variety of conditions indicate that individuals who are on a statin have lower morbidity and mortality rates than those not exposed to a statin. These data sets are observational in nature. It is unclear whether overall physician treatment in statin-treated patients is different (ie, better) compared to those not exposed to statins. The increased use of appropriate congestive heart failure therapy in the statin group suggests that this may be a factor; that is, that care in general was better and more evidence-based in the statin group. There are a variety of intracellular effects of HMG CoA reductase therapy, known as pleiotropic actions. Thus, endothelial function and nitric oxide availability are improved, cytokines and other inflammatory markers are diminished, and coronary plaque may be stabilized by statins. This report adds to a wide variety of data in the literature that come to the same conclusion, although with widely disparate diagnoses. Clearly, at the very least, physicians should pay particular attention to current lipid guidelines, and make sure that congestive heart failure patients are appropriately treated, particularly for LDL cholesterol lowering, and that individuals with heart failure should not to be considered ineligible or poor statin candidates because of their primary illness. ■

Statins Prevent Post-Operative Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Synopsis: *Treatment with atorvastatin 40 mg/d, initiated 7 days before surgery, significantly reduces the incidence of postoperative AF after elective cardiac surgery with cardiopulmonary bypass and shortens hospital stay.*

Source: Randomized Trial of Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery: Results of the ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery) Study. Patti G, et.al. *Circulation*. 2006; 114:1455-1461.

PATTI AND COLLEAGUES FROM THE CAMPUS BIO-Medico University in Rome report the results of Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery study (ARMYDA-3). The study was

designed to test whether atorvastatin significantly reduced the incidence of atrial fibrillation after cardiac surgery. All patients undergoing cardiac surgery with cardiopulmonary bypass over a 30-month period at a single institution were evaluated. Patients with a history of atrial fibrillation, a need for emergency cardiac surgery, previous or current treatment with statins, renal or hepatic disease, or any inflammatory disease were excluded. The final study group consisted of 200 patients, 99 of whom were randomized to placebo and 101 to atorvastatin, 40 mg per day, beginning 7 days before the scheduled surgery. Patients undergoing all types of cardiac surgery were eligible.

Patients were monitored continuously in the intensive care unit and then in a telemetry unit for at least 6 days after the operation. C-reactive protein levels were assessed in all patients before surgery and every 24 hours postoperatively until discharge. After discharge, patients were scheduled for weekly visits in the outpatient clinic for the first month. The primary end point of the trial was the incidence of postoperative atrial fibrillation. Atrial fibrillation was defined as an electrocardiographically documented episode that lasted greater than 5 minutes or required earlier intervention. Total arrhythmia burden was quantified on the basis of a number of atrial fibrillation episodes per patient, the ventricular response, the postoperative response to recurrence, and the total duration of the episodes. Secondary end points included the length of postoperative stay and the incidence of major adverse cardiac and cardiovascular events. The authors correlated the pre- and post-operative peak C-reactive protein (CRP) levels with the occurrence of atrial fibrillation and attempted to identify variables that were predictors of outcome.

The 2 groups were well matched. The mean age was slightly older than 65 and approximately two-thirds of patients were male. Almost one-third of patients had chronic obstructive pulmonary disease and 25% were smokers. The mean left ventricular ejection fraction was slightly greater than 50%. Most had coronary revascularization only, but 25% had valve surgery with or without revascularization.

Postoperative atrial fibrillation occurred in 35 (35%) of 101 patients in the atorvastatin arm vs 56 of 99 (57%) patients in the placebo arm ($P = 0.003$). Among patients who developed atrial fibrillation, there was no difference in the mean ventricular response, time to occurrence, or the total duration of episodes. In patients who developed atrial fibrillation, intravenous infusion of amiodarone restored sinus rhythm in all patients. No patients had recurrence of the arrhythmia after termination of the first episode.

The mean postoperative stay was significantly lower in the atorvastatin group (6.3 ± 1.2 days) vs the placebo group (6.9 ± 1.4 days). Major adverse cardiac events, however, were similar. The baseline preoperative CRP levels did not differ between the groups and did not change after surgery. However, CRP levels were higher among those patients who developed atrial fibrillation regardless of randomization assignment. By multivariate analysis, age over 65, systemic hypertension, aortic atherosclerosis, and an elevated CRP were predictors of postoperative atrial fibrillation. Therapy with beta blockers, atorvastatin, and in particular, the combination of these two agents predicted freedom from atrial fibrillation.

The authors conclude that the ARMYDA-3 Trial demonstrates that treatment with atorvastatin reduces the incidence of new onset postoperative atrial fibrillation and produces a short but significant decrease in hospital stay. They urge that routine statin therapy be employed in these patients.

COMMENTARY

This is a relatively small study and there are some limitations in the trial design. However, it does illustrate that there is a developing paradigm shift in the management of arrhythmias. Formerly, most antiarrhythmic drug therapy concentrated on agents which blocked cardiac ion channels. Beta blockers, ACE inhibitors and statins have now been shown to have profound effects on arrhythmia frequency, and, in fact, may be more effective overall than traditional antiarrhythmic drugs.

There are some limitations to the data presented here. It is surprising that two-thirds of the patients screened were not previously treated with statins before undergoing bypass surgery. The incidence of postoperative atrial fibrillation in the control group is also quite high, much higher than in many other similar trials. Despite these limitations, however, the data are provocative and point out that strategies directed at the factors which predispose towards arrhythmias should always be considered first and traditional antiarrhythmic drugs used only as needed.

First-Line Treatment for Atrial Flutter in the Elderly: Ablation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *RFA should be considered a first-line therapy even after the first episode of symptomatic AFL.*

Source: Da Costa A, et al. Results From the Loire-Ardeche-Drome-Isere-Puy-de-Dome (LADIP) Trial on Atrial Flutter, a Multicentric Prospective Randomized Study Comparing Amiodarone and Radiofrequency Ablation After the First Episode of Symp-tomatic Atrial Flutter. *Circulation.* 2006;114: 1676-1681.

DA COSTA AND COLLEAGUES REPORT A MULTICENTER, randomized trial comparing amiodarone and radiofre-

quency ablation in elderly patients with atrial flutter. The study was named the LADIP Trial after the first letters of the cities of the investigators. Patients older than age 70 were considered eligible for the trial if they presented with a first episode of atrial flutter that appeared to be consistent with classic counterclockwise right atrial macroreentry. This was confirmed in most patients by electrophysiologic study or by entrainment with right atrial pacing. They could not have been previously treated with antiarrhythmic drugs. Patients were randomly assigned to either radiofrequency ablation or amiodarone as initial therapy. The electrophysiologic studies and catheter ablations were performed using standard approaches. Either an 8 mm tip electrode catheter or an irrigated 5 mm tip thermocouple catheter were used for the ablations. The procedural end point was bidirectional isthmus block. Patients in the amiodarone group were assigned to electrical cardioversion. Initially, this was attempted with a right atrial catheter that was used to confirm right cavotricuspid isthmus entrainment. If rapid pacing did not restore sinus rhythm, external or internal cardioversion was applied. Patients then received amiodarone at a dose of 400 mg for 4 weeks starting 7 days before the atrial pacing. After that, amiodarone was continued at a dose of 200 mg daily.

During follow-up, patients were seen at periodic intervals. Arrhythmia monitoring was performed using a combination of history, 12 lead electrocardiograms, and Holter monitoring. The Holter monitoring was performed using an event recorder that performed a continuous ECG analysis combined with automatic storage of abnormal events detected in a 20-minute solid state memory. Manual activation of the Holter storage was also possible. The primary end point was time to occurrence of atrial flutter confirmed by ECG. Time to first occurrence of atrial fibrillation was a secondary end point. Episodes lasting longer than 10 minutes were considered clinically significant but episodes lasting from one minute to 10 minutes were quantified. Patients in the amiodarone group who developed recurrent atrial flutter went on to receive radiofrequency ablation.

One hundred and four patients were entered into the trial with 52 entered into both the radiofrequency ablation and the amiodarone groups. In the radiofrequency ablation group, bidirectional block was achieved in 100% of patients with a mean radiofrequency application time of 12.8 + 13 minutes. There were no procedure-related complications. In the amiodarone group, 12 patients converted to sinus rhythm during the initial 7 days of amiodarone, 17 were converted by intraatrial pacing and 22 by internal or external direct current cardioversion. After a mean follow-up of 13 ± 6 months, atrial flutter recurred in 2 of 52 (3.8%) radiofrequency ablation patients, in contrast to 15 of 51 (29.5%) amiodarone treated patients. Significant symptomatic or asymptomatic atrial fibrillation of greater than 10-minute duration occurred in 25% of the group 1 patients and 18% of the group 2 patients. When all atrial fibrillation episodes were taken into account, including asymptomatic episodes of less than 10 minutes duration, documented by ECG, the 2 groups did not differ significantly with 29% of the radiofrequency ablation patients and 20% of the amiodarone patients having episodes. Patients who had prior episodes of atrial fibrillation were more likely to have recurrent atrial fibrillation after the first episode of atrial flutter.

There were 6 deaths in the radiofrequency ablation group and 8 deaths in the amiodarone treated group. Most deaths were noncardiovascular in origin and not apparently related to the atrial arrhythmia. Five other major clinical events occurred in the amiodarone treated group: hypothyroidism in 2, hyperthyroidism in one, and symptomatic sinus node dysfunction in 2.

The authors conclude that in patients 70 years or older, radiofrequency ablation should be considered to be the preferred therapy for classic atrial flutter. Although the risk of subsequent atrial fibrillation remains high, the procedure can be performed with a low risk of complications and the strategy does not subject patients to the adverse effects of long-term drug therapy.

COMMENTARY

Atrial flutter is a particularly bothersome arrhythmia. Unlike atrial fibrillation during which concealed conduction of the AV node allows rate control to be achieved in most patients, rate control in atrial flutter is often difficult and most patients usually must be cardioverted out of atrial flutter to control their symptoms. Over the last decade, electrophysiologists have learned that the common type of atrial flutter involves a counterclockwise macroreentrant circuit in the right atrium. This circuit often passes through a critical isthmus between the inferior vena cava and the tricuspid annulus. Placing an ablation line through this area terminates atrial flutter and prevents its recurrence. In experienced hands, the procedure is very safe and highly successful. Recurrence rates which were high when the procedure was first introduced have fallen dramatically with the introduction of either cooled-tip or large tip radiofrequency ablation catheters. In the study here, the LADIP investigators confirmed that radiofrequency ablation is an effective initial therapy for patients with atrial flutter. The major disappointment with the procedure involves the relatively high incidence of atrial fibrillation during follow-up. The pathologic bases for atrial fibrillation and atrial flutter are similar. Therefore, it is not surprising given the patient cohort here included only those over age 70 that the incidence of atrial fibrillation during follow-up was similar in the 2 groups. However, the observations

that the risk of any arrhythmia recurrence is no higher and that the complications associated with the radiofrequency ablation procedure are lower than those associated with chronic antiarrhythmic therapy argue that the invasive approach should be the preferred strategy for patients who present with typical atrial flutter. ■

Simple Measures to Prevent Vasovagal Syncope

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Physical counterpressure maneuvers are a risk-free, effective, and low-cost treatment method in patients with vasovagal syncope and recognizable prodromal symptoms, and should be advised as first-line treatment in patients presenting with vasovagal syncope with prodromal symptoms.*

Source: van Dijk N, et al. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope. *J Am Coll Cardiol*. 2006;48:1652-1657.

VASOVAGAL SYNCOPE IS A COMMON AND OFTEN DISabling disorder that lacks solid evidence-based treatment options. Thus, the Physical Counterpressure Maneuvers trial was conducted in 15 centers worldwide that treat syncope patients. Patients with recurrent typical vasovagal syncope with prodromal symptoms were recruited. Patients with overt heart disease, orthostatic hypotension and other causes of syncope were excluded. Patients with negative head-up tilt-table tests were included if their symptoms were classic. Patients were randomized to standardized optimal conventional therapy with or without training in physical counterpressure maneuvers. Conventional therapy included the admonition to increase salt and water intake, but not drug therapy. The physical maneuvers included leg crossing, handgrip and arm tensing without doing the Valsalva maneuver. The primary endpoint was the risk of recurrent syncope. Conventional therapy was applied to 117 patients and counterpressure to 106. Mean follow-up of the 208 patients (mean age, 38 years) not lost to follow-up was 14 months. Syncope recurred 142 times in the conventional group and 76 in the counterpressure group for a recurrence rate of 51% and 32%, respectively (RR .36, CI = .11–.53, P = .005). Presyncopal events were similar in both groups, 74% vs 83% (P = NS). Women had more recurrences then men, but the effectiveness of counterpressure was not different. Patients preferred arm tensing to handgrip and leg tensing. There were no injuries during follow-up. The authors concluded that physical counterpressure maneuvers are an effective risk-free, low-cost method to prevent vasovagal syncope in patients with prodromal symptoms and should be the therapy tried first.

■ COMMENTARY

Recurrent vasovagal syncope is often treated by drugs such as fludrocortisone to increase salt and water retention, but this therapy has not been subjected to a randomized controlled trial. Vasoactive drugs have not been superior to placebo in trials and pacemaker studies have had mixed results. Thus, this is the first randomized controlled trial that has shown benefit from any treatment for vasovagal syncope. Unfortunately, although simple, it cannot be applied to everyone with vasovagal syncope. Some patients may have no prodromal symptoms or symptoms that are too brief to act quickly to prevent syncope. The authors believe this may explain some of the treatment failures, since not every syncopal event is the same in a patient. They may have prodromal symptoms, but not always.

There are some limitations to the study. Not everyone got carotid sinus massage, so some with this condition could have been in the trial and explained some of the treatment failures. Also, some may have inadvertently performed a Valsalva maneuver which would thwart the benefit of muscle tensing. Only the patients were blinded, so physician interpretation of recurrences could have been biased in some cases. In addition, head-up tilt-table testing was not positive in everyone, so some could have had other causes of syncope that would not respond to muscle tensing. There may have been some patients in the trial that could have responded to drug therapy.

Despite these limitations, this was an impressive study with a number needed to treat of 5 to prevent one recurrent syncopal event. It makes sense to try this simple approach first in appropriate patients before embarking on drug therapy or devices. ■

Prognosis of LBBB

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Hypertension, ischemic heart disease, left ventricular hypertrophy, ST-T abnormalities, and an increased cardiothoracic ratio were associated with LBBB.*

Source: Imanishi R, et al. Significance of Incident Complete Left Bundle Branch Block Observed Over a 40-year Period. *Am J Cardiol.* 2006;98:644-648.

LEFT BUNDLE BRANCH BLOCK (LBBB) IS BELIEVED TO more often imply cardiac disease than right BBB, but long-term follow-up studies are scant. Thus, this group

from Japan studied 17,361 atomic bomb survivors in Hiroshima and Nagasaki biannually since 1958 and present their 40-year follow-up of the 110 who developed LBBB during follow-up. Nine with LBBB at the first exam were excluded. For each LBBB case 5 age- and sex-matched controls were selected. Controls with pacemaker or atrial fibrillation were excluded since none of the LBBB subjects had these conditions at onset of LBBB. The rate of LBBB was 675 in men and 692 in women per 100,000 population (< 1%). Mean age at onset of LBBB was 70 for men and 68 for women and the occurrence of LBBB increased with advancing age. The presence of underlying hypertension, ischemic heart disease, and enlarged heart on chest X-ray were statistically more common with LBBB onset. Surprisingly all cause mortality was not different between the LBBB group and controls, nor was the mean age at death. However, death due to heart failure (16 vs 7%) and myocardial infarction (9 vs 3%) were more common with LBBB as compared to controls. In the Cox multivariate regression analysis, LBBB remained an independent predictive variable for heart failure death. The authors concluded that LBBB is predictive of death due to heart failure, but does not predict all-cause mortality independent of underlying clinical factors.

COMMENTARY

The strength of this study is the 40-year follow-up of subjects without LBBB at study entry. Although this is an unselected general population of about equal numbers of men and women, they were all exposed to radiation. Nevertheless, the occurrence of LBBB overall was rare, but did increase with advancing age. Also, it was about equal in men and women. Not surprisingly LBBB was strongly associated with ischemic heart disease, hypertension and an enlarged heart on x-ray. With subject evaluations every 6 months, this study provides the clinical diagnosis of the subject at the time of LBBB onset, which is an unique strength of this study. So, the old adage that LBBB means heart disease is present as compared to right BBB where it usually is not seems to be true. Of course this only applies to complete right BBB, as incomplete right BBB is almost always due to right ventricular enlargement.

The weaknesses of this study are those common to large-scare epidemiologic studies in that measurements are parsimonious. For example, there are no echocardiograms, cardiac catheterizations nor autopsies. The data are all from history, physical exam and chest X-ray, and there is certainly death certificate bias. Nevertheless, this is a useful study that points out the high mortality from heart failure in LBBB patients. Perhaps this is due to dyssynchrony and could be reduced by cardiac resynchronization. ■

CME Questions

29. Patients with severe heart failure can be treated with:
a. heart transplantation.
b. long term LVAD support.
c. short term LVAD, plus aggressive drug therapy.
d. All of the above

30. First line treatment for atrial flutter in the elderly is:
a. ablation
b. amiodarone
c. procainamide
d. beta blocker

31. Statins may reduce mortality in patients with:
a. ischemic cardiomyopathy
b. idiopathic dilated cardiomyopathy
c. hypertrophic cardiomyopathy
d. A and B

32. Which of the following have antiarrhythmic effects?
a. Statins
b. Beta blockers
c. ACE inhibitors
d. All of the above

33. Which of the following may prevent vasovagal syncope?
a. Increased salt and water intake
b. Diuretics
c. Isometric limb muscle contraction
d. A and C

34. Development of LBBB on ECG predicts:
a. all-cause mortality
b. heart failure mortality
c. earlier age at death
d. All of the above

Answers: 29. (d) 30. (a) 31. (d) 32. (d) 33.(d) 34. (b)

CME Objectives

The objectives of *Clinical Cardiology Alert* are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To present the current data regarding outpatient care of cardiac patients. ■