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INSIDE

Aortic Stenosis—New Insights

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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

Source: Pellikka PA, et al. Outcome of 622 Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up. *Circulation*. 2005;111:3290-3295.

THIS IS A LONG-TERM OBSERVATIONAL REPORT OF A LARGE Mayo Clinic cohort of patients with hemodynamically significant, but asymptomatic, aortic stenosis (AS). Their previous analysis of 113 of these patients with a mean follow-up of 20 months was published in 1990. This study consists of 622 adults seen at the Mayo Clinic, all over 40 years of age, and with a peak systolic echo velocity > 4 m/s on Doppler echo. The study period was 1984 to 1995, with an initial population of 2800, reduced to 622 individuals with no other significant cardiac disease or who remained asymptomatic during follow-up. All patients were asked to return at 6 or 12 months. Clinical information was also obtained by a mailed questionnaire, telephone interview, or review of medical records. The analysis included the probability of development of new cardiac symptoms, the probability of death, and the probability of remaining free of cardiac death or aortic valve surgery. The cohort had a mean age of 72 ± 11 years; approximately two-thirds were men. Mean aortic peak velocity was 4.4 ± 0.4 m/s, and the mean gradient was 46 ± 11, with a mean aortic valve area (AVA) of 0.9 ± 0.2 cm^2. The duration of follow-up was a mean of 5.4 ± 4 years, during which 50% of the patients developed symptoms of angina, dyspnea, or syncope. Freedom from cardiac symptoms was 82% at one year, 67% at 2 years, and 33% at 5 years. Valve area and the presence of LVH were independent predictors of symptom development. Fifty-seven percent of the entire cohort underwent aortic valve surgery, of whom 221 developed symptoms and 131 remained

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Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer.

asymptomatic. Thirty percent of the entire cohort died during follow-up, but only 19% were cardiac deaths. The probability of remaining free of cardiac death and aortic valve surgery was 80% at one year, 63% at 2 years, and only 25% at 5 years. Age, renal failure, inactivity, and aortic valve velocity were predictors of mortality. Of the entire group, 30% had a baseline peak velocity > 4.5 m/s. These individuals had a relative risk (CRR) of 1.3 for developing symptoms and a 1.5 RR for AV surgery or cardiac death. There were 11 sudden deaths in patients who did not become symptomatic prior to demise. In asymptomatic and unoperated patients, freedom from cardiac death was 99%, 98%, and 93% at one, 2, and 5 years. Pellikka and colleagues state, "the course of these patients was not benign," and "the likelihood of developing cardiac symptoms was high, with only 33% of the cohort remaining symptom-free and unoperated at 5 years." Also, "asymptomatic, severe AS has a small but real risk of sudden death." Predictors of symptoms included AVA and LVH. Risk factors for all cause mortality included age, chronic renal failure, inactivity, and aortic valve velocity. Pellikka et al conclude that clinical and echo characteristics were imperfect for identifying unoperated subjects at risk of death.

COMMENTARY

A 1997 study established an aortic velocity of > 4.0 m/s as severe AS. The current study identifies a velocity of > 4.5 m/s having the highest likelihood of symptoms; thus, the more severe the obstruction to outflow, the worse the outcome in this group of asymptomatic patients. Pellikka and colleagues suggest that a peak velocity > 4.5 m/s "might be considered for prophylactic aortic valve replacement." Surgery was highly protective in this study. Pellikka et al comment that mortality for aortic valve replacement today should be less than 5% at high volume centers; peri-operative mortality in the Mayo Clinic population was 1.4%. They state that most patients with severe, asymptomatic AS will develop symptoms within 5 years. AVA and LVH are predictors of symptoms. Sudden death without preceding symptoms was rare (approximately 1% per year) and cannot be predicted by clinical parameters.

This is a useful report that adds new information to several recent publications on AS. Follow-up was as long as 10 years, and the studied parameters in this population are quite familiar. In essence, an aortic peak velocity > 4 is a sensitive predictor in unoperated subjects at 5-year status; the Mayo Clinic suggests that a higher peak velocity, greater than 4.5, should trigger consideration of a prophylactic surgical strike. Previous studies have included other variables of outcome, but there is now a substantial database utilizing peak aortic velocity as an important discriminating factor. The present report has identified aortic valve area and LVH as particularly important characteristics associated with long-term outcomes. It would appear reasonable to consider aortic valve replacement in individuals with a very small valve area and the presence of LVH. All major outcomes, including unoperated, freedom from cardiac symptoms, freedom from cardiac death without surgery, remaining asymptomatic without surgery or death, demonstrate excellent outcomes at 1 to 2 years, but with a marked drop-off by the fifth year of follow-up of subjects remaining asymptomatic with freedom with cardiac death. In the true elderly, individuals that are virtually housebound, or the occasional patient with chronic renal failure, the use of aortic valve velocity may help with decision making. When symptoms occur, surgery is mandated for almost all individuals.

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Aortic Valve Prosthesis-Patient Mismatch (Size Doesn't Make Much Difference)

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Synopsis: *A majority of patients report improvement in functional quality of life early after AVR. Similar functional recovery was demonstrated for patients along the full spectrum of valve sizes indexed to body size, even for values considered to represent severe mismatch for patient size. Factors other than prosthesis-patient size influence functional quality of life early after AVR.*

Source: Koch CG, et al. Impact of Prosthesis-Patient Size on Functional Recovery After Aortic Valve Replacement. *Circulation*. 2005:111:3221-3229.

PROSTHESIS-PATIENT MISMATCH RELATES TO A SMALLER prosthetic valve size than the relevant native valve, in relation to a patient's body size. There is much literature dealing with this subject. This report from the Cleveland Clinic represents 1014 patients who underwent aortic valve replacement between 1995 and 1998. Koch and colleagues' hypothesis was that a "smaller valve size relative to body size would be reflected by less improvement and functional qual- ity of life post-operatively." They used the Duke Activity Status Index (DASI) to objectively evaluate a patient's physical activity level and capacity. Patient were evaluated using multiple statistical techniques. In this population, 88% of the mechanical valves implanted were St. Jude Medical, representing 16% of all prostheses. Other valves included the CarboMedics mechanical valve and the Carpentier-Edwards stented bovine pericardial valve. Patients underwent a pre-op DASI evaluation at 6 and 12 months; the early post-op follow-up DASI score was used for the major data analysis and represented an average interval from surgery to survey follow-up of 8.3 months.

Results: Most patients demonstrated an improvement in functional quality of life. Of interest, those with lower baseline DASI scores, reflecting a poor level of function, had greater improvement in DASI scores than those who began with a higher baseline function, which usually stayed the same or decreased. There was no pattern or relationship found between valve size and follow-up DASI score. Valve orifice size was an unreliable predictor. However, female sex, need for transfusion, older age, and elevated creatinine were all related to "less favorable post-operative functional recovery."

COMMENTARY

The rationale for aortic valve replacement (AVR) includes improvement in functional capacity and quality of life. This was the case with the majority of patients in this study, and comparable to many other reports. Koch et al point out that prosthesis-patient mismatch occurs in many individuals because of a small aortic annulus. The definition of mismatch itself is variably described in different publications. The literature is inconsistent regarding the impact of mismatch on clinical outcomes; some but not all studies report an increase in mortality and morbidity, but others do not confirm any relationship with survival and prosthesis mismatch. Prior data suggest that patients with larger valves have greater improvement in the postoperative period. Koch et al's hypothesis was that a smaller valve size indexed to body size would be related to lower functional scores; however, "measures of indexed valve size were unrelated to postoperative functional recovery period." Other factors related to functional recovery include female sex (reported in many investigations and not well understood) and increasing age, with a lower likelihood of elderly patients achieving a high postoperative DASI score. Other reports have not shown an age relationship to post-op functional capacity. A ceiling effect clearly limited many unimpaired individuals from being able to improve their DASI score, as they were highly functional to begin with.

In conclusion, while overall quality of life is improved in most patients undergoing AVR, prosthesis-patient size does not appear to influence functional recovery after AVR. A number of pre-operative variables (transfusion, age, female sex, higher creatinine) imparted "considerable emphasis on post-operative functional recovery."

This information should be useful to the general cardiologist in helping to make decisions regarding AVR. Female gender and advanced age did adversely impact postoperative functional recovery; this is not new news, but needs to be taken into account when decisions are made in elderly women whether to proceed with aortic valve surgery.

It is common in echo studies to observe a high aortic gradient raising the question of prosthetic valve mismatch. Twenty-fifth to 77 percentile data are available for all valve sizes, as well as aortic valve peak and mean gradients in this paper. ■

Amiodarone vs Sotalol for 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: *Amiodarone and sotalol have a similar efficacy for converting atrial fibrillation to sinus rhythm, that the drugs do not significantly impair electrical cardioversion and that amiodarone is superior to sotalol which, in turn, is better than placebo, for maintaining sinus rhythm.*

Source: Singh BN, et al. Amiodarone Versus Sotalol for Atrial Fibrillation. *N Engl J Med*. 2005;352:1861-1872.

THE SOTALOL AMIODARONE ATRIAL FIBRILLATION EFFICACY Trial (SAFE-T) was a double-blind, placebo-controlled comparison of sotalol and amiodarone in patients with persistent atrial fibrillation. Patients were eligible for enrollment if they had been in atrial fibrillation for at least 72 hours, were receiving anticoagulation, and had a calculated creatinine clearance above 60 mL/minute. Patients with class III or class IV heart failure, intolerance of beta blockers, or a history of a long QT syndrome were excluded. Randomized patients were assigned to receive amiodarone, sotalol, or placebo on an outpatient basis. Amiodarone dosage was 800 mg per day for 14 days, 600 mg per day for the next 14 days, 300 mg per day for the first year, and 200 mg per day afterwards. The sotalol regimen was 80 mg twice daily for the first week and 160 mg twice daily afterwards. Follow-up was obtained by clinic visits every 4 weeks, and transtelephonic ECG recordings weekly. If spontaneous conversion had not occurred by day 28 after randomization, direct current transthoracic cardioversion was performed. The primary outcome measure was the time to the first recurrence of atrial fibrillation after sinus rhythm had been restored. Quality of life, exercise capacity, and adverse events were also monitored.

A total of 665 patients underwent randomization: 267 to amiodarone, 261 to sotalol, and 137 to placebo. Eighty-one patients withdrew consent and 28 were lost to follow-up. Since this was a Veterans Administration study, 98.9% were men. The mean age was 67.1 ± 09.3 years.

During the first 28 days of drug therapy, 27.1% of patients in the amiodarone group, compared to 24.2% in the sotalol group and 0.8% of patient in the placebo group, converted to sinus rhythm. Patients who did not convert by day 28 underwent cardioversion. The cardioversion was unsuccessful in 28% of the patients in the amiodarone group, 27% of patients in the sotalol group, and 32% of patients in the placebo group. Including both spontaneous and electrical conversions, the total conversion rates were 79.8%, 79.9%, and 68.2% in the amiodarone, sotalol, and placebo groups, respectively. Using the primary end point of time to first recurrence of atrial fibrillation, amiodarone was more effective than sotalol, and both drugs were more effective than placebo. Using an intention to treat analysis, 48% of patients in the amiodarone group. 68% in the sotalol group, and 87% in the placebo group had a recurrence by one year. In a treatment-received analysis, the corresponding values were 35%, 60%, and 82%. The primary end point, median days to recurrence, was strikingly different between the 3 groups. In the intention to treat analysis, it was 487 days for the amiodarone group vs 74 days for sotalol and 6 days for placebo. Amiodarone was superior to sotalol in all subgroups, except that there was only a trend among patients with known ischemic heart disease. Changes in quality of life and exercise capacity were not different based on drug assignment. However, patients who remained in sinus rhythm overall had superior scores for physical functioning, general health, and social functioning and had more improvement in exercise capacity than did those who redeveloped persistent atrial fibrillation.

Minor bleeding events were more common in the amiodarone group (8.33 per 100 patient years) than in the sotalol group (6.37) or the placebo group (6.71). Major bleeding episode rates were 2.07, 3.10, and 3.97 per 100 patient years in the 3 groups. The rates for major and minor strokes were similar between the 3 groups. There were 2 cases of nonfatal pulmonary toxicity in the amiodarone group and one in the placebo group. One case of nonfatal torsades de pointe occurred in the sotalol group. Overall, there were 13 deaths (6 sudden) in the amiodarone group, 15 deaths (8 sudden) in the sotalol group, and 3 deaths (2 sudden) in the placebo group. The trend toward increased mortality in the combined drug treated groups (4.36 per 100 patient years vs 2.84 per 100 patient years) did not achieve statistical significance ($P = 0.13$).

Singh and colleagues conclude that amiodarone and sotalol have a similar efficacy for converting atrial fibrillation to sinus rhythm, that the drugs do not significantly impair electrical cardioversion, and that amiodarone is superior to sotalol which, in turn, is better than placebo, for maintaining sinus rhythm.

COMMENTARY

SAFE-T is the largest comparative trial of amiodarone

in patients with persistent atrial fibrillation. It clearly shows that amiodarone is more effective than sotalol, and that both drugs are more effective than placebo in maintaining sinus rhythm over an intermediate period of follow-up. Both drugs were surprisingly well tolerated in terms of reported side effects. The population studied here was fairly typical for an atrial fibrillation population, but the mean ejection fraction was close to 50%, and only about 25% of patients had any symptoms of heart failure. Patients were also screened for renal function, and only patients with well preserved renal function could be included in the trial. Despite this, Singh et al noted a slight, albeit, nonsignificant trend towards increased mortality during drug therapy, and when the data were examined in an intention to treat analysis, no improvement in quality of life was seen. These data could be interpreted that patients who can be maintained in sinus rhythm are likely to do better than if they are left in atrial fibrillation, but that the overall population will not benefit. These data, therefore, are in agreement with the large rate control vs rhythm control trials which showed slight mortality trends in favor of a rate control strategy.

SAFE-T confirms results of prior trials in patients with atrial fibrillation. Based on the accumulated data, it seems reasonable to follow a symptom based approach. Patients who are asymptomatic with rate control do not require trials of antiarrhythmic drug therapy and cardioversion. Patients who are symptomatic, however, may benefit from drug therapy and a cardioversion strategy, even though many patients will develop persistent atrial fibrillation over time. ■

Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction or Heart Failure

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *The absolute risk for sudden death or cardiac arrest is greatest in the early period after myocardial infarction, and the event rate declines significantly over time.*

Source: Solomon SD, et al. Sudden Death in Patients With Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both. *N Engl J Med*. 2005;352:2581-2588.

The valsartan in acute myocardial infarction Trial (VALIANT) was a randomized, controlled trial comparing valsartan, captopril, or combined therapy with both agents in over 14,000 patients with a recent myocardial infarction that had been complicated by heart failure and/or left ventricular systolic dysfunction. For the purpose of this analysis, patients who received an ICD before randomization were excluded. During follow-up, all deaths were reviewed in a blinded fashion. Sudden death was explicitly defined as death that occurred "suddenly and unexpectedly" in a patient in an otherwise stable condition.

During a median follow-up period of 24.7 months, 1067 of 14,609 (7%) patients experienced either sudden death (903) or were resuscitated after cardiac arrest (164). Five of the patients who were resuscitated after cardiac arrest died on the date of resuscitation. Of the 164 patients who were resuscitated, 108 (66%) remained alive at 6 months and 93 (57%) were alive at the end of the trial. Patients who died suddenly or who had cardiac arrests were significantly older, had higher baseline systolic and diastolic blood pressures, baseline heart rates and Killip class, had a lower left ventricular ejection fraction, were more likely to have a history of diabetes or hypertension, and were less likely to have received reperfusion therapy, amiodarone, or beta blockers. However, there were only relatively minor differences when the 1067 patients in the sudden death group were compared to the 1905 patients who died from causes other than sudden death. Sudden death and cardiac arrest were most common during the first 30 days after myocardial infarction. During this time period, 126 patients died suddenly and 72 patients were resuscitated from cardiac arrest. This represented 19% of all such events during the entire trial. The sudden death/cardiac arrest event rate was 1.4% per month during this period. From one month to 6 months, the event rate was 0.5% per month, from 6 months to 12 months the event rate was 0.27% per month, from one through 2 years, the event rate was 0.18% per month, and from 2 to 3 years, the event rate was 0.14% per month. The increased early incidence of sudden death or cardiac arrest was most prominent in patients with the lowest ejection fractions. Among patients with an ejection fraction of 30% or less, the incidence rate during the first 30 days for sudden death or cardiac arrest was 2.3% per month. During the entire course of the trial, out of 399 of the 3852 patients, 10% with an ejection fraction of 30% or less, died suddenly, or had cardiac arrest, compared with 295 of the 4998 patients (6%) with an ejection fraction between 31% and 40%, and 119 of the 2406 (5%) patients with an ejection fraction of more than 40%. Although the relative rates differed based on the ejec-

tion fraction, the time-dependent feature was seen in all groups. For the entire group, the rate of sudden death or cardiac arrest was more than 6 times as high in the first month as after one year.

Solomon and colleagues conclude that the absolute risk for sudden death or cardiac arrest is greatest in the early period after myocardial infarction, and that the event rate declines significantly over time. Solomon et al concluded that their data confirmed the high risk of sudden death early after myocardial infarction, and argue that these data suggest the need to consider early implementation of strategies to prevent sudden death after myocardial infarction.

COMMENTARY

These data from the VALIANT trial confirm earlier observations that the overall mortality and, in particular, the sudden death mortality rate after myocardial infarction, is highest during the first 30 days after the event. Unfortunately, prophylactic antiarrhythmic drug therapy has not been shown to be effective in this population, and the single ICD trial that focused on this group (DINAMIT) also showed no benefit. In the latter trial, although ICD therapy decreased the incidence of arrhythmic death, this was compensated for by an increased number of deaths from other causes. As a result, the overall mortality was unchanged. This is supported by observations from the MADIT-II trial that have also showed that there was greater benefit in patients with more chronic myocardial infarction. In MADIT-II, no benefit was seen in patients who entered this trial within 18 months of their last myocardial infarction. Primarily on the basis of DINAMIT, currently those guidelines do not allow reimbursement for ICD implants within 40 days of myocardial infarction. How to manage high risk patients during this period, therefore, becomes a significant clinical issue, since neither antiarrhythmic drugs nor ICD therapy has shown benefit.

The patients in VALIANT all received an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, or both. Most also received beta blockers and aspirin. However, only a minority received either primary percutaneous intervention at the time of their infarct or thrombolytic therapy, and any form of revascularization was significantly more common in those among the long-term survivors. Therefore, one interpretation of these data and the data from DINAMIT and MADIT II might be that the risk for sudden death in the first month after myocardial infarction is different than during the more chronic phases. During this phase, mortality might be dominated by recurrent infarction, ischemia, or heart failure. In this setting, any benefits from an ICD might be blunted. For now, physicians caring for such patients should concentrate on optimizing therapy for ischemia and heart failure. ■

Biventricular Pacing ECG

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *BiV capture can be accurately detected by observing the R/S ratio in leads V1 and I of the 12-lead ECG.*

Source: Ammann P, et al. An Electrocardiogram-Based Algorithm to Detect Loss of Left Ventricular Capture During Cardiac Resynchronization Therapy. *Ann Intern Med*. 2005;142:968-973.

WITHOUT RESORTING TO CALLING SOMEONE IN WITH the programmer appropriate to your patient's device, it is often difficult to tell if biventricular (biV) pacing is working correctly. Thus, Ammann and colleagues sought to develop 12-lead ECG criteria for loss of left ventricular capture, a frequent problem that could cause a deterioration of the patient's symptoms. They started with 10 patients who they switched from right to biV pacing, and observed the 12-lead ECG changes. They developed an algorithm to detect left ventricular (LV) capture: R/S amplitude in V1 > 1, yes, LV capture; no, look at lead I, R/S > 1, yes, LV capture, no, means RV pacing only. Then they had 2 blinded, general cardiologists test the algorithm in 54 different patients with biV pacing, which was turned on and off. All patients had left bundle-branch block before pacing, the LV lead was placed in the coronary sinus and the RV lead at the apex. The algorithm detected biV pacing 93% of the time and RV pacing 94% of the time. The algorithm was 100% accurate for detecting biV pacing when the coronary sinus catheter was in the diagonal branches of the anterior interventricular vein or the middle cardiac vein, but only 90% of those in the posterior and left marginal veins. Ammann and colleagues concluded that biV capture can be accurately detected by observing the R/S ratio in leads V1 and I of the 12-lead ECG.

COMMENTARY

Loss of LV capture by dislodgement of the coronary sinus lead is a potential cause of heart failure decompensation in a biV-paced patient. The ability to detect it on the surface ECG without resorting to the programmer, which is often not readily available in a busy general cardiology or heart failure clinic, is of value. The algorithm described in this study is simple and works fairly well with sensitiv-

ities and specificities of 90% or better. It is based upon starting with lead V1 over the right ventricle. If there is LV activation, the R wave vector should be directed at V1 with an R/S > 1. Sometimes, the RV activation obscures LV activation in V1 so when the R/S in V1 is < 1, then lead I needs to be examined. With LV activation the vector should be away from lead I with an R/S > 1. There are some limitations. The algorithm only works if the underlying rhythm was left bundle-branch block. Also, certain programmed intervals and delays may obscure LV activation, but these will be detected by the programmer when you refer the patient for lack of LV pacing. In addition, this algorithm was developed in patients with RV apex pacing, as is usually done with an AICD-biV pacer device. Other RV lead placements may not be as accurate. With these limitations in mind, this algorithm seems to be a useful screening device for failure of LV capture in biV pacing, and should reduce the number of programmer checks required for managing heart failure patients. ■

BNP for Differentiating Constrictive Pericarditis vs Restrictive Cardiomyopathy

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *BNP levels are significantly elevated in RCM patients as compared to CP patients, and should be a useful noninvasive marker to distinguish the 2 conditions.*

Source: Leya FS, et al. The Efficacy of Brain Natriuretic Peptide Levels in Differentiating Constrictive Pericarditis From Restrictive Cardiomyopathy. *J Am Coll Cardiol*. 2005;45:1900-1902.

DIFFERENTIATING CONSTRICTIVE PERICARDITIS (CP) from restrictive cardiomyopathy (RCM) is frequently challenging and often involves multiple imaging strategies and a full invasive hemodynamic evaluation. Of course, the effort is worthwhile because CP is potentially curable, but an easier diagnostic marker would be welcome. Leya and colleagues hypothesized that brain natriuretic peptide (BNP) may not be elevated in CP since the myocardium is constrained from dilating, but would be in RCM due to increased filling pressures in non restrained chambers. They studied 11 consecutive patients being invasively evaluated for these conditions and measured BNP at the time of the invasive evaluation. The hemodynamic evaluation was extensive and involved transseptal catheterization and fluid challenges when necessary. The diagnostic standard for CP was the presence of intracardiac and intrathoracic disassociation and right and left ventricular pressure discordance. Surgical findings were also considered.

Results: In 6 patients, CP was diagnosed (4 confirmed at surgery, 2 refused surgery); 5 had RCM. Right and left heart resting hemodynamics were not different between the 2 groups. However, BNP levels were higher in the RCM patients (826 vs 128 pg/mL, $P < .001$) and there was no overlap in each group's range of values (639 to 1060 vs 50 to 186 pg/mL). Leya et al concluded that BNP levels are significantly elevated in RCM patients as compared to CP patients and should be a useful noninvasive marker to distinguish the 2 conditions.

COMMENTARY

This is a new, novel use for BNP that promises to be helpful to the clinician. In CP, BNP was < 200 pg/mL; in RCM it was > 600 pg/mL in this study. Although encouraging, there are a few caveats. First, this is a small study (n = 11) and highly select. They excluded patients with significant valvular disease, those suspected of having effusive constrictive disease, such as heart transplant patients, and radiation therapy patients. Second, all 11 patients had a definite diagnosis based upon invasive hemodynamics and some by surgical confirmation (4/6 with CP). One could argue that no patient should go to surgery without definite hemodynamic evidence of CP and a thickened pericardium by imaging. If imaging was done in this study, the results were not presented. So where would BNP be useful? I can think of a few scenarios. The patient with indeterminate hemodynamics and unclear imaging may be an example. In a patient with classic RCM on echocardiography, it may be reassuring to have a high BNP if you are not going to pursue an invasive evaluation. Only further experience will define the usefulness of BNP in this situation. Hopefully, its use will not lead to more unnecessary testing as troponins have in other hospitalized patients. ■

New POTS Treatment?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Acute acetylcholinesterase inhibition reduced standing heart rate and symptoms in POTS patients.*

Source: Raj SR, et al. Acetylcholinesterase Inhibition Improves Tachycardia in Postural Tachycardia Syndrome. *Circulation*. 2005;111:2734-2740.

THE TREATMENT OF POSTURAL TACHYCARDIA SYNDROME (POTS) is often challenging, and beta-blockers do not always produce the desired effect. Thus, Raj and colleagues hypothesized that acetylcholinesterase inhibition may increase parasympathetic tone both at the ganglionic and post ganglionic receptors, resulting in bradycardia. POTS inclusion criteria were met by 17 patients, and included symptoms of orthostatic intolerance, a heart rate rise of > 30 bpm within 10 minutes of standing in the absence of orthostatic hypotension, and elevated standing norepinephrine levels (> 2.8 nmol/L). Patients were studied in a metabolic research unit where fluid, electrolyte, and drugs were tightly controlled. On separate days, placebo or pyridostigmine 30 mg po was given. Symptoms were logged before drug administration, and 2 and 4 hours afterward. Of the 17 subjects, 15 completed both limbs of the study (12 females). Resting, sitting heart rate was not different between the 2 treatments (87 bpm), but standing heart rate was significantly lower on active treatment (100 vs 111 bpm, $P < .001$) at 2 hours but not at 4 hours (104 vs 109 bpm). Also, symptom score decreased on treatment (23 to 15, $P < .05$) at 4 hours, but not on placebo (19 to 20). Blood pressure was not significantly altered in any position by active drug. Raj and colleagues concluded that acute acetylcholinesterase inhibition reduced standing heart rate and symptoms in POTS patients.

COMMENTARY

POTS predominantly is a disease of women in their childbearing years and, though rare, causes considerable disability, especially for a young mother. Although usually self-limiting, it often persists for months. Thus, effective treatment would be desirable. Unfortunately, the standard approach of using the same drugs that we use for neurocardiogenic syncope (beta-blockers, clonidine, fludrocortisone) is not always very effective and may cause excessive fatigue and other intolerable side effects. The novel approach in this study is attractive theoretically, and this study provides proof that the concept is sound. Whether pyridostigmine will be effective in longer-term therapy is unknown. There are reports of its successful use in other forms of orthostatic intolerance, but the main potential limitation is gastroenterologic symptoms due to increased intestinal motility. The drug is available as 60 mg tablets and is mainly used for myasthenia gravis. Dosing for that disorder is 60-120 mg po q 3-8 hours, so it is not convenient to take. One advantage over clonidine and beta-blockers is that it does not lower blood pressure. At this point, it may be worth trying in refractory POTS patients, but selecting the correct dose and dosing interval will be an experiment. ■

CME Questions

7. Which is most related to functional outcomes after valve replacement surgery?
a. Low indexed valve area
b. Female sex
c. Older age
d. B and C

8. Which is most successful at maintaining sinus rhythm in patients with atrial fibrillation?
a. Amiodarone
b. Sotalol
c. Beta blockers
d. Digoxin

9. The risk of sudden cardiac death post MI is greatest:
a. during the first month.
b. one month to 6 months.
c. 6 months to a year.
d. after the first year.

10. Asymptomatic patients with significant aortic stenosis should be considered for surgery if there is:
a. calcified leaflets.
b. a peak velocity >4.5m/sec.
c. LVH.
d. B and C

Answers: 7. (d); 8. (a); 9. (a); 10. (d)

CME Objectives

The program's objectives 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 test; and

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