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INSIDE

BNP vs Tissue Doppler for LV Filling Pressure

ABSTRACT & COMMENTARY

Synopsis: mitral Doppler E/Ea correlates better with PCWP than BNP and is more specific for predicting PCWP > 15 mm Hg.

Source: Dokaimish H, et al. *Circulation.* 2004;109:2432-2439.

A SIMPLE NON-INVASIVE METHOD OF ESTIMATING LEFT VENTRICular (LV) filling pressure in critically ill patients, would be desirable. Hence, Dokaimish and colleagues sought to compare echo Doppler methods to serum B-type natriuretic peptide (BNP) levels for estimating pulmonary capillary wedge pressure (PCWP). They screened 57 consecutive patients, admitted to the intensive care unit, who had pulmonary artery catheters placed for clinical reasons. Exclusion criteria included atrial fibrillation, severe mitral regurgitation, and acute myocardial infarction, which eliminated 7 patients. The principal echo Doppler method was the ratio of the peak early mitral inflow velocity (E) to the early diastolic tissue-Doppler (Ea) of the mitral annulus (average of septal and lateral velocities). The admitting diagnoses, in the 50 patients, include heart failure, respiratory failure, and hemodynamic instability post major surgery or trauma. The objective of the study was to determine ability of E/Ea and BNP levels to predict PCWP > 15 mm Hg.

Results: Log BNP was weakly correlated with PCWP (r = .32, *P* =.02) but E/Ea correlated more strongly (r = .69; *P* < .001). The optimal cut point for E/Ea to predict PCWP > 15 mm Hg was 15; sensitivity 86%, specificity 88%. The optimal BNP cut-off was 300 pg/mL; sensitivity 91%, specificity 56%. In the 36 patients with cardiac disease, E/Ea performed even better in predicting PCWP > 15 mm Hg; sensitivity 92%, specificity 91% vs sensitivity 92%, specificity 51%, for BNP. Whereas, in the patients without cardiac disease, BNP appeared stronger at predicting PCWP > 15 mm Hg; sensitivity 81%, specificity 83% vs sensitivity 74%, specificity 72% for E/Ea. In the 9 patients who had all 3 measures repeated after 48-hours of treatment, E/Ea correlated better with change in PCWP than BNP did (r = .87; *P* < .003 vs r = -.59; *P* = .39, respectively). Dokaimish and colleagues concluded that in patients admitted to an Intensive Care Unit, mitral Doppler E/Ea correlates better with PCWP than BNP and is more spe-

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cific for predicting PCWP > 15 mm Hg. Also, E/Ea is most accurate in patients with cardiac disease, whereas, BNP was more accurate in patients without cardiac disease.

COMMENT BY MICHAEL H. CRAWFORD, MD

Today, intensive care units are mainly filled with severely ill multisystems disease patients, end-stage heart failure patients, or post-surgical patients with hemodynamic instability. Most are intubated, at least initially, and many have rhythm disturbances. The use of indwelling pulmonary artery catheters has declined in such patients because their risk outweighs their benefit. Thus, an accurate non-invasive technique for determining who has a high LV filling pressure would be of value. BNP is very attractive because it is a simple blood test, and has performed well in the Emergency Department setting for determining who is in heart failure when it is not obvious clinically. The more complicated patient in today's Intensive Care Units is a different challenge, and the results of this study show mixed results for BNP. In the absence of structural heart disease, it was pretty good at determining who had a PCWP > 15 mm Hg, but in those with structural heart disease, it had a low specificity, and hence, a low positive predictive value. This is undoubtedly because BNP is influenced by other factors besides filling pressure in patients with cardiac disease, such as left atrial size, ejection fraction, LV mass, etc. If one can be certain that the patient has no structural heart disease, then BNP is an easy way to predict who is fluid overloaded, and in such patients the cut point is 250 pg/mL. However, if cardiac status is uncertain, then an echocardiogram needs to be done. Thus, some have suggested that a high BNP should be used to screen for who needs the more expensive echocardiogram.

In this study, mitral Doppler E/Ea performed best overall for predicting PCWP and especially PCWP > 15 mm Hg, but this is partly because 70% of the patients had cardiac disease. Mitral E/Ea may not have performed as well in a population with less heart disease. The result is not surprising since mitral E/Ea directly measures early flow across the mitral valve in diastole, and normalizes it for annular motion. Early mitral flow is most related to the early pressure gradient, which is heavily dependent on left atrial pressure. Interestingly, other echo Doppler filling parameters did not perform as well as mitral E/Ea in this study. LV, EF, mitral E velocity deceleration time, pulmonary venous systolic filling fraction, and the difference between pulmonary venous velocity A-wave duration and mitral A-wave velocity duration, all had correlation coefficients between 0.5-0.6 compared to E/Ea at r = .69. However, in those patients with E/Ea in the gray zone (8-14), consideration of these other parameters help correctly classify the patients with regard to PCWP.

The use of BNP serially, to assess response to therapy, was evaluated in 9 patients in this study, who had repeat measurements at 48 hours. The results were similar to other reports that have shown little value for BNP. It is not surprising that mitral E/Ea would change immediately with PCWP, but BNP, which is influenced by so many other factors, may lag in response to positive hemodynamic changes. ■

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Optimal Frequency of BNP Testing

ABSTRACT & COMMENTARY

Synopsis: *At this time, BNP seems to be a useful initial test that should not be repeated during short hospital stays.*

Source: Wu AHB, et al. *Am J Cardiol.* 2004;93: 1562-1563.

SINCE BNP IS ELEVATED IN PATIENTS WITH CONGESTIVE heart failure, serial testing may be useful for deter-

mining the response to therapy. In order to establish the usefulness of serial testing, knowledge of the assay variability is required. Thus, Wu and colleagues performed a retrospective study of laboratory records at 2 large metropolitan hospitals to determine the optimal frequency of BNP measurements for this purpose. The study population consisted of 2748 samples from 1926 patients admitted for heart failure, approximately one-third of whom had ≥ 2 BNP measures done in the first week after hospitalization. Only patients with ≥ 2 BNP measures at 22 days were included. Their previous studies, in normal subjects and stable heart failure subjects, suggested that a difference of 100% in BNP values was the biologic variation cut point.

Results: The likelihood of finding a significant difference in BNP values was lowest when blood was retested the next day (22%) or in 2 days (39%). The likelihood of finding a significant difference was highest when samples were 6 or 7 days apart (50%). Thereafter, the percentag, with a significant difference, fell off again. Overall, two-thirds of significant differences were decreases in BNP, suggesting that most patients improved. Wu et al concluded that daily, or every other day, monitoring of BNP, in patients admitted with heart failure, does not appear warranted.

COMMENT BY MICHAEL H. CRAWFORD, MD

This observational study, based upon laboratory records, is sobering, considering the widespread use of serial BNP testing today. However, it is in line with other recent studies, including the one discussed above, that have not shown value for the indiscriminate serial use of BNP testing in hospitalized patients. The results are also in line with our thinking about heart failure treatment. Some patients will get immediate benefit from diuretics, which may be reflected in the one-fourth to one-third of patients whose BNP values do change significantly over the first 2 days, but many hospitalized patients (50% in this study) may take 6 or 7 days to improve enough to overcome the effects of cardiac structural changes on BNP level, such as left atrial dilation. Also sobering is the magnitude of change required to be biologically significant, 100%. This value is based upon their previous work showing that a significant serial BNP change in normal subjects was 129% and for stable heart failure subjects was 77%. They used the average difference of 100% for this study. Had they used the lower value, perhaps BNP would have looked somewhat better, but I doubt it would have materially changed the results. At this time, BNP seems to be a useful initial test that should not be repeated during short hospital stays. ■

More Help Estimating Filling Pressures by Echo/Doppler

ABSTRACT & COMMENTARY

Synopsis: *Reflex tachycardia, during a Valsalva maneuver, is a sign of normal LV filling.*

Source: Marrill CA, et al. *J Am Soc Echocardiogr.* 2004;17:634-637.

Despite the overall usefulness of mitral Doppler flow velocity profiles for estimating diastolic function of the left ventricle, differentiating normal from pseudo-normal filling patterns is difficult. The response to a Valsalva maneuver has been suggested to be of help in this differentiation, but in some patients, the Valsalva induced tachycardia fuses the mitral E and A velocities, rendering analysis impossible. Marrill and colleagues from the Mayo Clinic hypothesized that tachycardia induced by a Valsalva maneuver may be of diastolic value in and of itself. Thus, they studied 77 patients referred for left heart catheterization. During catheterization, left ventricular pre A-wave pressure in diastole was recorded, as was the heart rate and aortic pressure during Valsava maneuver. The baseline ECG R-R interval, divided by the shortest R-R interval during the Valsalva maneuver, was the R-R ratio.

Results: A pre A-wave LV diastolic pressure of 18 mm Hg was chosen as the cut point; 58 patients had pressures < 18, and 19 had higher pressures. An R-R ratio of > 1.1 had a positive predictive value of 94% for a pre A-wave pressure < 18. In patient subgroups with LV ejection fraction above or below .50, age above or below 60, and presence or absence of beta blocker therapy, the results were not significantly different. In diabetics, the positive predictive value dropped to 75%, but there were only 4 patients in this group. Marrill et al concluded that reflex tachycardia, during a Valsalva maneuver, is a sign of normal LV filling.

COMMENT BY MICHAEL H. CRAWFORD, MD

Differentiating normal from pseudo-normal mitral Doppler flow velocity patterns can be aided by a Valsalva maneuver. The Valsalva maneuver transiently reduces LV filling by increasing intra-thoracic pressure during the strain phase. In normals, reduced LV filling results in

diminution of both the E- and A-waves of mitral inflow velocity equally. However, in some normals, the resulting reduced stroke volume leads to reflex tachycardia and fusion of the E- and A-waves. This study shows that the increase in heart rate itself is a sign of normal filling pressures. In patients with high filling pressures, the reduced filling volume during Valsalva decreases the E-wave, but accentuates the A-wave, revealing the abnormal filling pattern. Since many patients with high filling pressures are on a flat starling curve, the reduced filling changes stroke volume very little, so no reflex tachycardia is seen. However, an abnormal Valsalva response can be due to confounders such as older age, beta blockers, and autonomic dysfunction (diabetes). Thus, an abnormal Valsalva response is of less diagnostic value than a normal one, but in the former case, the E- and A-wave characteristics can be interpreted. One caveat is that the heart rate response must be continuously assessed so the fastest rate is detected, usually during the strain or just after. Later, the increased stroke volume, post release of the strain, results in a bradycardia in normals. Another is that a falsely abnormal test can be seen with inadequate strain. The adequacy of the strain can be assessed by a mouth pressure gauge or by feeling the abdominal muscles contract. ■

Echo Diagnosis of Prosthetic Valve Endocarditis

ABSTRACT & COMMENTARY

Synopsis: *Mild, perivalvular regurgitation cannot be used as a diagnostic criteria for prosthetic valve endocarditis.*

Source: Ronderos RE, et al. *J Am Soc Echocardiogr.* 2004;17:644-649.

EVEN WITH TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE), the diagnosis of infectious endocarditis is difficult in patients with prosthetic valves. Thus, Ronderos and colleagues sought to determine the accuracy of various findings indicative of prosthetic valve endocarditis. They evaluated 58 episodes of suspected prosthetic valve endocarditis in 49 patients: 32 patients had definite endocarditis by Durack's criteria and 17 did not, by surgical criteria or long-term clinical follow-up (8-38 months). TEE features that distinguished the definite endocarditis groups were: valve dehiscence (4 episodes), pseudo-aneurysms (3), fistulae (2), and moderate-to-severe perivalvular regurgitation (15). These findings were not present in the non endocarditis group. Apparent vegetations were seen in 17 episodes of definite endocarditis and 1 negative patient. Perivalvular abscesses were seen in 19 positive cases and 1 negative case. Mild perivalvular regurgitation was seen in only 1 positive case, but 14 negative cases. Using the above findings, with the exclusion of mild perivalvular regurgitation, resulted in a positive predictive value for diagnosing endocarditis of 94%, and a negative predictive value of 96%. TEE findings were confirmed at operation in all but 2 patients: 1, with a TEE finding of vegetation, had a degenerated bioprosthetic valve, and 1 perivalvular abscess by TEE, was sterile at surgery. Mortality in the definite endocarditis group was 34%, but echo findings did not predict death. Ronderos et al concluded that mild perivalvular regurgitation cannot be used as a diagnostic criteria for prosthetic valve endocarditis.

COMMENT BY MICHAEL H. CRAWFORD, MD

Prosthetic valves are strong echo reflectors and produce reverberation and shadowing artifacts that challenge the diagnostic accuracy for findings of endocarditis. Also, various non-infective surgical sequelae, such as sutures and hematomas, reduce the accuracy of diagnosing vegetations and abscesses. In addition, small amounts of perivalvular leaks are not uncommon because of suture failure or perivalvular atheromatosis plaques. Thus, even on TEE, diagnosing prosthetic valve endocarditis can be difficult. Yet, this diagnosis is critical since surgery is almost always the appropriate treatment.

This study provides some useful experience that helps with the diagnosis of prosthetic valve endocarditis. Fistulae, pseudo-aneurysms, dehiscence, or 3-4+ perivalvular regurgitation all had a 100% positive predictive value; whereas, mild perivalvular leaks had a positive predictive value of 6%. They defined pseudo-aneurysms as perivalvular cavities with flow in and out of them. Abscesses (cavities > 10 mm without blood flow) and vegetations were highly predictive, but there were false positives. Interestingly, vegetations, the hallmark of native valve endocarditis, were only seen in 50% of the definitely positive cases. One case that appeared to have a vegetation turned out to be a severely degenerated bioprosthetic valve. Although not observed in this study, sutures and small perivalvular strands can cause confusion as well.

The study has some limitations. The small number of cases requires that the 100% positive predictive values be taken with a grain of salt. One more case could drop these values. Also, 80% of the valves were

mechanical, so conclusions about bioprosthetic valve endocarditis should be interpreted cautiously. ■

Gender Differences in Ventricular Arrhythmia Recurrence

ABSTRACT & COMMENTARY

Synopsis: *These data should force us to look at factors other than the traditional variables we have used to assess risks among patients with a history of ventricular arrhythmias.*

Source: Lampert R, et.al. *J Am Coll Cardiol.* 2004;43:2293-2299.

Lampert and colleages report a single center study on the influence of gender on ventricular arrhythmia recurrence in patients with coronary disease and implantable cardioverter defibrillators (ICDs). Lampert et al reviewed data on 650 consecutive patients who received an ICD with the ability to store diagnostic electrograms for ventricular tachycardia (VT) or ventricular fibrillation (VF) events between June 1990 and June2000. Only patients who had both coronary artery disease and an ICD, which could store multiple (>10) episodes, were included in the study. As a result, 399 patients formed the final study cohort. A large number of clinical and electrocardiographic variables were analyzed as potential predictors of arrhythmia recurrence. The variables analyzed included electrocardiographic, clinical, angiographic, and electrophysiologic study data.

The final group consisted of 340 men and 59 women. Women tended to be older, had a higher prevalence of diabetes and hypertension, and had a slightly higher left ventricular ejection fraction. However, aneurysms were seen in 38% of women vs only 16% of men. Electrocardiographic and electrophysiologic parameters were similar between men and women. During an average follow-up of 30 ± 22 months, sustained VT or VF, requiring ICD therapy, occurred in 52% of men and 34% of women. Men also experienced more total VT and VF events, and had more electrical storms (3 or more episodes within 24 hours, 31% vs 7%). In a multivariate analysis including a number of factors, men remained more than twice as likely as women to undergo any VT or VF event (odds ratio, 2.20, 95% confidence interval 1.02-4.90). Other factors independently associated with VT or VF events at presentation were sustained VT, VT induction at electrophysiologic study, and absence of immediate or remote revascularization. Lampert et al then go on to discuss potential mechanisms for these findings. They conclude that both genders benefit from ICD therapy, but that the risk of recurrence is higher in men.

■ COMMENT BY JOHN P. DiMARCO, MD, PhD

Numerous studies have shown that age-adjusted sudden death rates are lower in women than they are in men, and that even after an initial episode of cardiac arrest or ventricular tachycardia, rates of recurrence are lower in women than in men. However, those prior observations do not usually control for patients with only coronary artery disease. This interesting paper by Lampert et al suggests that even among patients with coronary disease, a gender difference in arrhythmia recurrence can be demonstrated.

The reasons for this are uncertain. Lampert et al, in this paper, considered numerous clinical factors, and could not identify any important characteristics that would seem to favor women over men. Importantly, diabetes and hypertension were more common in women than in men, and men were more likely to have undergone revascularization. These factors would have been expected to lower the risk in men. Men were slightly more commonly treated with beta blockers than were women, but this also should have been a factor in their favor. One would think that all of these factors would have worked to lower frequency of events among men than women, but the opposite was seen here.

There are many social and economic factors that have been implicated in sudden death rates. Teasing out the role of these factors from clinical trial data is often very difficult. However, the data presented by Lampert et al are quite provocative. They should force us to look at factors, other than the traditional variables we have used, to assess risks among patients with a history of ventricular arrhythmias. ■

High Incidence of Pacemaker Syndrome in VVIR Pacing

ABSTRACT & COMMENTARY

Synopsis: *The basic conclusion is that we should give the patient just what he or she needs and the devices we implant should be designed to fit the patient.*

Source: Link MS, et.al. *J Am Coll Cardiol.* 2004;43:2066-2071.

The mode selection trial (MOST) was a randomized, clinical trial comparing atrially based (usually DDD or DDDR) pacing to VVIR pac-

ing in patients with sinus node dysfunction. This report details the incidence and significance of pacemaker syndrome associated with VVIR pacing in this study.

Patients were eligible for inclusion in MOST if they had a clinical diagnosis of sick sinus syndrome and could receive a dual chamber pacemaker utilizing a transvenous approach. In the study, all patients received a dual chamber pacemaker. Patients were then randomized by programming to either rate modulated ventricular (VVIR) or dual chamber (DDDR) pacing. Baseline data included assessment of retrograde atrial activation and blood pressure responses during ventricular pacing. Quality-of-life measures including the SF-36, the self-reported Quality of Life, a disease specific activity scale, and a functional utility scale were also collected. Initial programming was recommended to be a lower rate of 60 bpm, with rate modulation adjusted to a heart rate of 90 bpm to 110 bpm after a one minute brisk walk. Follow-up was performed at regular intervals. The primary end point in MOST was the first occurrence of stroke or death, but the occurrence of pacemaker syndrome was an important, prespecified secondary end point. Pacemaker syndrome was defined by new or worsened dyspnea, orthopnea, elevated JVP, rales, or edema with VA conduction during ventricular pacing or by symptoms of dizziness, weakness, presyncope, and a 20 mmHg reduction of systolic blood pressure when the patient had VVIR pacing compared with atrial pacing or sinus rhythm. If pacemaker syndrome was diagnosed, programming steps to either lower the ventricular rate or to decrease the sensor driven rate were made. However, if symptoms did not resolve, patients could be crossed over from VVIR pacing to DDDR pacing.

In MOST, 996 patients were randomized to VVIR pacing. The median age was 74 years, and 48% were female. New York Heart Association functional class III or IV heart failure was present in 15%, AV conduction disease, including complete heart block, was present in 26%. Among these patients, 182 (18.3%) met criteria for pacemaker syndrome during the course of the study. By life table analysis, the incidence of pacemaker syndrome was 13.8% after 6 months, 16% at 1 year, 17.7% at 2 years, 19% at 3 years, and 19.7% at 4 years. Among the baseline factors which were analyzed as a predictor of the development of pacemaker syndrome, only a reduced baseline heart rate and a higher programmed ventricular rate were significantly associated with development of pacemaker syndrome. In multivariate analysis, only a higher percentage of beats paced was an independent predictor ($P = 0.0001$; HR, 1.22 for each 10% increase). The development of pacemaker syndrome was associated with significant decreases in quality of life, as measured by multiple instruments. After cross-over to an atrially-based pacing mode, these parameters improved. The most striking improvements were in measures of energy and physical function.

Link and colleagues conclude that pacemaker syndrome is a common complication of VVIR pacing in patients with sinus node dysfunction. Since prediction of this syndrome is difficult, they argue that all patients with sinus node dysfunction should receive atrial based pacing.

COMMENT BY JOHN P. DiMARCO, MD, PhD

There have been a number of trials comparing various modes of pacing in patients with AV block and sinus node dysfunction. After several years of follow-up, these studies have not shown dramatic changes in mortality or stroke incidence, but they have demonstrated a decreased incidence of atrial fibrillation. The development of pacemaker syndrome is another reason why atrially based systems seem to be preferable, but as admitted by Link et al, the data in the literature are inconsistent. In the MOST trial, all patients received a dual chamber pacemaker, and the pacing mode was known to both physicians and patients. Therefore, in patients who knew they were randomized to VVIR pacing and had nonspecific complaints, it was relatively easy for Link et al to try an atrially based pacing mode since a surgical procedure was not required. Although criteria for the diagnosis of pacemaker syndrome had been specified, they may also be seen with other conditions. In MOST, almost 20% of the patients developed what Link et al considered to be a pacemaker syndrome. In contrast, other studies, in which surgical procedures would have been required to change pacing mode, have reported an incidence of pacemaker syndrome of only 2% to 3%. The real incidence probably lies somewhere between these extremes. It is also important to note that many patients with sinus node dysfunction can be managed with just atrial pacing systems. Atrial pacing has the advantage that it requires only a single lead system and avoids the complication of ventricular dyssynchrony that may be induced by right ventricular apical pacing.

There are new functions that are being incorporated into the next generation of pacing that address at least this last issue. Pacemakers can now search the AV interval and try to attempt to minimize the proportion of beats that are ventricularly paced. One system, currently available only in Europe, essentially has separate sensing systems to provide atrial pacing most of the time and ventricular pacing only if heart block develops. These innovations lower the risk that heart block will develop in a patient programmed for just atrial pacing. In conclusion, there is now consistency among all studies that atri-

al pacing, when possible, is preferable. In the absence of AV block, avoidance of ventricular pacing is also preferable. The basic conclusion is that we should give the patient just what he or she needs, and the devices we implant should be designed to fit the patient. Ventricular pacing in patients with sinus node dysfunction then becomes the choice only when other factors preclude effective atrial pacing. ■

Prevention of Cardiovascular Events After Percutaneous Coronary Intervention

ABSTRACTS & COMMENTARY

Synopsis: *Folic acid and B vitamins may yet be proven to have a positive role through decreasing HC levels, but enthusiasm for such an approach is no longer appropriate.*

Sources: Lange H, et.al. *N Engl J Med.* 2004;350:2673-2681. Herrmann HC. *N Engl J Med.* 2004:350:2708-2710.

Homocysteine (HC) has long been considered a putative risk factor for coronary disease (CAD). Many physicians prescribe routine folate supplementation, along with vitamin B6 and B12, to lower serum levels of HC, with the hopes of decreasing vascular risk. Considerable interest arose several years ago when Schnyder and colleagues reported on decreased coronary restenosis rates following angioplasty in individuals given folate therapy (*N Engl J Med.* 2001;345:1593-1600). Subsequently, other negative trials have appeared, and on balance, there is considerable confusion in the published literature as to whether HC is or is not a modifiable risk factor for CAD, particularly in the realm of percutaneous revascularization. This European study represents investigators from Bremen, Germany, Zwoll, and The Netherlands, who enrolled 636 patients in a randomized, placebo-controlled study assessing the efficacy of folic acid and B vitamins in individuals undergoing PCI with stenting. Standard restenosis indices were assessed using blinded, quantitative coronary-angiography. Reference diameter, minimal luminal diameter, and lesion length were calculated at base line, as well as at a 6 month angiogram. Individuals with clinical symptoms could undergo angiography prior to the scheduled follow-up procedure. Restenosis was defined as greater than 50% of luminal diameter; late luminal loss, acute gain, and a loss index were calculated. Therapy consisted of an initial intravenous bolus dose of 1 mg of folic acid, 5 mg of vitamin B6, and 1 mg of vitamin B12, followed by daily oral administration of 1.2 mg of folic acid, 48 mg of vitamin B6, and 60 µg vitamin B12, vs placebo. Baseline characteristics were well matched; 20-25% were women; mean age was 61; 14% had diabetes; 30% smoked; and 60% had hypercholesterolemia. Forty percent of individuals had a previous MI or coronary bypass graft; 40% were on statins, 25% on ACE inhibitors, and 70% on beta-blockers; all received clopidogrel and aspirin. Routine follow-up angiography was scheduled at 6 months; target lesion revascularization (TLR) was recommended for restenosis of 75%-90%, 70 with symptoms or signs of ischemia, and in all patients when a stenosis exceeded 90%. Bare metal stents only were used. The primary angiographic end point was minimal lumen diameter within the target lesion at follow-up. The primary clinical endpoints were any event related to restenosis, including death, MI, and TLR. The results indicated that folate and vitamin B therapy did not reduce restenosis, compared to placebo; there even was a somewhat smaller 6-month-minimal lumen diameter in the treatment cohort. Women and diabetics, however, benefited from the experimental cocktail, as did individuals with high homocysteine levels (all NS). Clinically driven TLR was greater in the experimental group (7.6 vs 4.4%). The overall restenosis rate was 34.5% in the folate group, compared to 26.5 % in the placebo group $P = 0.05$. Lange and colleagues conclude that the data do not provide any evidence that folic acid therapy, for primary or secondary prevention of CAD, is potentially harmful, since folate did not increase the incidence in death or infarction. However, they caution that this therapy should be considered a double-edged sword in patients with stents, with both antiproliferative and proproliferative actions potentially linked to the vitamin cocktail. The lower rates of restenosis in folate-treated women, diabetics, as well as those with markedly elevated HC, remain to be evaluated in subsequent trials. Statin therapy had no effect on restenosis rates.

■ COMMENT BY JONATHAN ABRAMS, MD

This study, in addition to another recent publication (Genser D. *Am J Cardiol.* 2002;89:495-499), does not support that HC is a modifiable risk factor favoring decreased restenosis. The study was carefully performed and the data appear to be highly reliable. There was a biphasic clinical response to folate, with the overall folate cohort having a

smaller minimal lumen diameter than placebo at 6 months, but there was a suggestion of some benefit in women and diabetics (statistically insignificant). The treatment cocktail did lower HC levels from a mean of 12.2 µmol/L at baseline to 8.7 µmol/L at 1 month ($P < 0.001$), and 6 months ($P < 0.001$). Lange et al discuss the biochemical pathways by which HC can be metabolized. Research data that folate may promote intimal proliferation is provided, and the suggestion is made that PCI individuals without stenting may have a different mechanism of restenosis than those with stents, with the latter resulting in considerable smooth muscle cell matrix proliferation, and angioplasty alone, stimulating thrombus inflammation within the vascular cracks.

In the accompanying editorial by Herrmann, emphasis is placed on the use a cardioprotective cocktail in all patients who undergo PCI, as well as ". . . refocus on the underlying disease process in order to treat vulnerable plaques and atherosclerosis and prevent subsequent cardiac events and new and progressive atherosclerotic lesions." Thus, Herrmann recommends the use of aspirin, clopidogrel, statins, and ACE inhibitors, along with lifestyle recommendations including diabetes and hypertension control, smoking cessation, and exercise, for all patients who have receive a stent. I would emphasize that this recommendation is germane for all patients who have vascular disease, except for the, as yet, uncertain role of long-term clopidogrel. Herrmann's emphasis is shared by me, stressing that atherosclerosis is a "chronic progressive disease," and that PCI is but a short-term, albeit dramatic, intervention which should not deflect physicians and patients from focusing on long term consequences of disease progression and its stabilization.

This study also re-emphasizes the need for well-designed clinical trials in order evaluate benefits and risks of therapies that appear to be beneficial on the surface, but may indeed not be useful or safe. The estrogen replacement story is well known, as are the negative results of antioxidant vitamins, a list to which we now must probably add folic acid replacement. In all of these areas, there were robust, although mixed, data supporting efficacy of each agent, yet large, well-designed trials resulted in red faces across academia and clinical practice, and retractions in multiple guidelines. Folic acid and B vitamins may yet be proven to have a positive role through decreasing HC levels, but enthusiasm for such an approach is no longer appropriate. ■

CME Questions

6. Folate therapy is indicated for?
a. prevention of restenosis post angioplasty
b. reducing high homocysteine levels to prevent CAD
c. preventing fetal neural tube disorders in pregnant women
d. all of the above

7. In CAD patients, the risk of VT/VF is higher in?
a. men
b. women
c. equal in both
d. unknown

8. The preferred pacing system in patients with sinus node dysfunction is?
a. VVIR
b. DDDR
c. AAIR
d. AICD

9. Highly valuable signs of prosthetic valve endocarditis include?
a. valve dehiscence
b. fistulae
c. moderate to severe perivalvular regurgitation
d. all of the above

10. The Valsalva maneuver is useful for the echo diagnosis of?
a. cardiac tamponade
b. increased LV filling pressure
c. CAD
d. all of the above

11. The optimal timing of serial BNP values in heart failure patients is?
a. 1 - 2 days apart
b. 3 - 4 days apart
c. 6 - 7 days apart
d. 10 days apart

12. For estimating if PCWP is > 15 mm Hg in critically ill cardiac patients, which is superior?
a. BNP
b. mitral Doppler E/Ea
c. LV ejection fraction
d. Doppler pulmonary diastolic pressure estimate

Answers: 6 (c); 7. (a); 8. (b); 9. (d); 10. (b); 11. (c); 12. (b)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Cardiology Alert*. Send your questions to: Leslie Hamlin, *Clinical Cardiology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Cardiology Alert* via the internet by sending e-mail to leslie.hamlin@thomson.com. ■