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INSIDE

Low Gradient Aortic Stenosis

ABSTRACT & COMMENTARY

SINCE PATIENTS WITH LOW GRADIENT AORTIC STENOSIS ARE AT higher risk for surgical replacement, more information concerning whom to select for surgery is desirable. Monin and colleagues from 6 centers in France studied 136 symptomatic patients with aortic valve area < 1.0 cm^2, low cardiac index (< 3.0 l/min/m^2) and a mean aortic pressure gradient < 40 mm Hg. All patients underwent dobutamine stress echocardiography (DSE) to a maximum dose of 20 mcg/kg/min. Decisions regarding surgery were made by the referring physician, who had knowledge of the DSE results. The majority of patients were men (96) and the mean age was 72 years. Almost all the patients presented with heart failure symptoms, and mean left ventricular ejection fraction (LVEF) was 0.30. About half of the patients had angiographic coronary artery disease (CAD), and two-thirds exhibited contractile reserve by DSE (stroke volume increase > 20%). Aortic valve replacement was done in 70% of the patients, and overall operative mortality was 14%. However, in the group with contractile reserve by DSE, operative mortality was 5% vs 32% in those without. Concomitant coronary artery bypass graft (CABG) surgery was performed in 25-30% of the patients and was associated with an increase in operative mortality to 11% in the contractile reserve patients and 62% in those without. By multivariate analysis, independent predictors of operative mortality were lack of contractile reserve (odds ratio [OR] = 11) and baseline mean aortic pressure gradient < 20 mm Hg (OR = 5). Predictors of long-term survival were aortic valve replacement (OR = 0.3) and contractile reserve (OR = 0.4). Improved functional class postoperatively was more common in those with contractile reserve (84 vs 45%; P = .002). Monin et al concluded that in low gradient aortic stenosis patients with demonstrable contractile reserve, surgery is generally beneficial. In those without contractile reserve, surgery is less beneficial due to a high operative mortality. Thus, DSE is of value for planning management in patients with low gradient aortic stenosis (Monin JL, et al. *Circulation*. 2003;108:319-324).

COMMENT BY MICHAEL H. CRAWFORD, MD

In patients with a normal stroke volume, a mean aortic valve gradient of > 50 mm Hg corresponds to a valve area of < 1.0 cm^2. When

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the calculated valve area is < 1.0 but the mean gradient is < 40 mm Hg, stroke volume must be low unless there is some error in the measurements. Such patients usually have reduced LV function and are at higher risk for valve replacement surgery. However, if such patients have LV contractile reserve that can be demonstrated by dobutamine stimulation, their prognosis with surgery is relatively good. On the other hand, those without demonstrable contractile reserve, especially if their resting mean gradient is < 20 mm Hg or if they have CAD, usually have a high mortality with surgery. Thus, the decision to pursue surgery in those with these negative predictors is a difficult decision because such patients do not do well with medical therapy either.

The other potential use for dobutamine stress echo is the identification of patients with relative aortic stenosis. These are patients with nonsevere aortic stenosis and marked cardiomyopathy in whom the stroke effort of the LV is insufficient to open the calcified aortic valve fully. In such patients, aortic valve area increases with dobutamine as the stroke volume rises. By contrast, those with true fixed aortic stenosis do not show a change in valve area with increased stoke volume. Relative stenosis patients were unusual in this large series. Only 5-7 of 136 patients met various criteria for this category, which is too small a number to say much about their long-term outlook.

There are several limitations of this trial. First, it was nonrandomized with regard to surgery. Second, the referring physicians decided on surgery, and they had access to the dobutamine data. Despite these potential biases, the same proportion of patients with and without contractile reserve were sent to surgery (70%). Third, even though it was a relatively large trial among valve disease studies, the number of patients was too small to answer many of the questions posed by the data, especially with regard to who should have surgery withheld. The most solid conclusion of the study is that DSE is useful in low gradient aortic stenosis patients for deciding who should have surgery. ■

Grading Valve Regurgitation By Echo/Doppler

ABSTRACT & COMMENTARY

Synopsis: *The Task Force on Valvular Regurgitation recommends the integration of several different techniques for evaluating the severity of native valvular regurgitation for echocardiography.*

Source: Zoghbi WA, et al. *J Am Soc Echocardiogr*. 2003;16:777-802.

THE TASK FORCE ON VALVULAR REGURGITATION OF the American Society of Echocardiography, in conjunction with the ACC, AHA, and ESC, has published recommendations for evaluating the severity of native valvular regurgitation by echocardiography. Unfortunately, the task force did not come up with a simple foolproof system, and certainly, one cannot rely on any one measurement or assessment technique. Instead, they recommended the integration of several different techniques. They recommend starting with the most specific signs (> 90% specificity) complemented by less specific but supportive signs. If this initial assessment indicates that the regurgitation is clearly mild, then nothing further is done. If not, quantitative measurements are recommended to determine whether the regurgitation is moderate or severe. They acknowledge the use of crossover categories such as mild to moderate and moderate to severe but don't take a firm stand that this is necessary. Trivial is lumped in with mild and they don't try to distinguish them. They describe the various assessment and measurement techniques in detail and point out technical issues and pitfalls of each. This is important because when all the techniques are congruent, the assessment of

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Table

Mitral Regurgitation

Parameter	Mild	Severe MR
Specific		
Jet area	< 4 cm^2, < 20% LA	> 40% LA
Vena contracta width	< 3 mm	> 7 mm
Flow convergence	< 4 mm	> 9 mm
Supportive		
Pulmonary vein flow	systolic dominant	systolic reversal
Mitral inflow	A wave dominant	E wave dominant
CW Doppler	soft parabolic signal	dense, triangular signal
LV, LA size	normal	enlarged
Leaflet anatomy	normal, mild thickening	flail
Quantitation of Regurgitant Flow		
Regurg Volume (mL/beat)	< 30	> 60
Regurg Fraction (%)	< 30	> 50
EROA (cm^2)	< 0.2	> 0.4

CW=continuous wave Doppler; EROA=effective regurgitant orifice area; LA=left atrium; LV=left ventricle; MR=mitral regurgitation; Regurg=regurgitant.

regurgitation severity is easy, but when they are not, considerable expertise and judgment is required to know which assessments are valid for establishing the correct severity. Also, they point out that blood pressure can affect the severity of regurgitation and recommend its measurement with an assessment of valvular regurgitation. (See the condensed versions of their Tables for grading the severity of mitral and aortic regurgitation as either mild or severe; everything else is moderate.) Tricuspid and pulmonic regurgitation are also covered in the recommendations but not shown here.

COMMENT BY MICHAEL H. CRAWFORD, MD

This is an important step in extracting ourselves from the quagmire surrounding the estimation of valve regurgitation severity grading. I have personally seen several patients turned into cardiac cripples because valvular regurgitation, which would be graded as mild by these criteria, was called moderate to severe by well-meaning physicians. Some of the patients actually went on to have surgery because of symptoms that were not due to their mild valve disease. Although less frequently, I have seen severe regurgitation graded as moderate, which lead to an unnecessary delay in corrective surgery with the risk of irreparable left ventricular damage. Hopefully, these recommendations will push us to a higher standard in grading valvular regurgitation. However, this will only happen if echocardiographers find these recommendations helpful and actually use them. Unfortunately, they are not simple or easy, and most of them require some measurement to be made. Current reimbursement levels in echo don't cover the costs of this intensive series of measurements in all patients with valvular regurgitation. Zoghbi and colleagues recognize this and suggest that the most time-consuming and technically demanding measurements of regurgitation should be reserved for the cases where the distinction between mild to moderate or severe was involved. The obviously mild cases wouldn't require these more sophisticated measures. This makes sense and would probably eliminate measurements in two-thirds of patients. There are a few simple points that can be made from the recommendations. First, grading left heart regurgitation as severe requires left ventricular enlargement and also left atrial enlargement with mitral regurgitation, unless the regurgitation is acute. Of course, the left ventricle and left atrium can be enlarged for other reasons (eg, atrial fibrillation), so otherwise mild regurgitation isn't automatically moderate or severe if the left heart chambers are enlarged. Second, grading mitral regurgitation requires an attempt to measure flow convergence since it is 1 of 3 highly specific measures. Unfortunately, it is not always technically possible, especially if the regurgitation is eccentric. Third, interrogation of more remote vessels, such as pulmonary veins in mitral regurgitation and the descending aorta in aortic regurgitation, is helpful for confirming grading. Finally, if blood pressure is

Table 2

Aortic Regurgitation

Parameters	Mild MR	Severe MR
Specific		
Central jet width	< 25% LVOT	> 65% LVOT
Vena contracta	< 3 mm	> 6 mm
Descending aorta flow		
Reversal	none or brief	holodiastolic
Supportive		
Pressure half time	> 500 msec	< 200 msec
LV size	normal	> mild enlargement
Quantitation of Regurgitant Flow		
Regurg volume (mL/beat)	< 30	> 60
Regurg Fraction (%)	< 30	> 50
EROA (cm^2)	< 0.1	> 0.3

LVOT = left ventricular outflow tract

high, the patient's doctor should be contacted and advised to perform a repeat echo after it has been lowered to desirable range. I have seen left heart regurgitation decrease 1 full grade with therapy of hypertension. The 4 cardiology organizations are to be congratulated for tackling this difficult task; now it is up to the rest of us to implement their recommendations and start making some sense out of the morass we are in with valvular regurgitation grading. ■

Mitral Valve Repair vs Replacement

ABSTRACTS & COMMENTARY

Synopsis: *Mitral valve repair is associated with reduced hospital length of stay and increased in-hospital and long-term survival compared to mitral valve replacement. However, these benefits are not seen in those older than 60 or those patients requiring concomitant CABG.*

Sources: Thourani VH, et al. *Circulation*. 2003;108: 298-404; Enriquez-Sarano M, et al. *Circulation*. 2003; 108:253-256.

ALTHOUGH MITRAL VALVE REPAIR FOR MITRAL REGURgitation is gaining in popularity, there are little comparative data with mitral valve replacement. Thus, Thourani and colleagues performed a case-controlled observational study of the Emory University Hospitals surgical database, matching 625 patients undergoing mitral valve repair with 625 undergoing mitral valve replacement from 1984 to 1997. The presence of preoperative heart failure was higher in the mitral valve repair group as compared to the replacement group (56% vs 50%; $P = .02$), and more repair patients had a myxomatous valve (46% vs 39%; $P < .001$). Otherwise, the 2 groups were well matched. Almost all the patients had elective surgery (96%), and about 25% of both groups had concomitant coronary artery bypass graft (CABG) surgery. Crossover to replacement from repair during the initial hospitalization occurred in 47 of the 625 repair patients (7.5%). Hospital length of stay was significantly less in the mitral repair group (9.5 vs 12.3 days; $P < .001$), and in-hospital mortality was less in the repair group (4.3% vs 6.9%; $P < .05$). Overall, 10-year survival was higher in the repair group (62% vs 46%; $P < .001$). Survival at 10 years in those younger than 60 was higher with mitral valve repair (81% vs 55%; $P < .001$) but was not significantly different in those older than 60 (33% vs 36%). Survival at 10 years for those who had concomitant CABG was not significantly different in those with mitral repair vs replacement (28% vs 34%). Freedom from subsequent mitral valve replacement was higher in mitral valve repair patients (78% vs 66%; $P < .001$). The strongest multivariate correlates with long-term mortality were mitral replacement and left ventricular dysfunction. Thourani et al concluded that mitral valve repair is associated with reduced hospital length of stay and increased in-hospital and long-term survival compared to mitral valve replacement. However, these benefits are not seen in those older than 60 or those patients requiring concomitant CABG.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

The potential benefits of mitral valve repair for significant mitral regurgitation are lower risk of thromboembolism, and hence, less need for anticoagulation, and better preservation of left ventricular function as compared to mitral valve replacement. This study adds the information that not only operative mortality, but also long-term mortality, is reduced by repair as compared to replacement. However, they found that these benefits did not extend to patients older than 60 or with concomitant CABG. This conclusion is at variance with other studies where the benefits were more uniformly observed. The accompanying editorial is authored by representatives from the Mayo Clinic who have published their experience and disagree with the investigators on the exclusivity of the benefits. They point out that this study included a higher proportion of patients with rheumatic heart disease (25%) than is seen in US series. Such patients are difficult to repair when they are older. They also pointed out that many of the patients in this study may have had ischemic heart disease, where mitral valve repair is not known to be of benefit. Another problem with the study is that since it spanned more than 20 years, the earlier patients may have gotten more bioprosthetic valves before their limited durability was shown in long-term trials only recently published. Currently, most patients would receive a mechanical valve unless anticoagulation was contraindicated or not desired. Although some of these critiques may influence the interpretation of the study, it is a valuable addition to our knowledge base and shows the superiority of mitral valve repair for mitral regurgitation. Thus, whenever feasible, mitral valve repair should be recommended and patients sent to centers with experience with this technically challenging procedure. Naturally, younger patients with myxomatous valves will be expected to do very well, but repair should not be automatically denied to older patients with

rheumatic or ischemic mitral regurgitation. These patients require careful evaluation, and perhaps surgery should be reserved for those with symptoms clearly due to their mitral regurgitation. ■

Are Lipid-Lowering Drugs Also Antiarrhythmic Drugs?

ABSTRACT & COMMENTARY

Synopsis: *Lipid-lowering therapy is associated with a decrease in recurrent VT/VF and improvements in all-cause and cardiac mortality.*

Source: Mitchell LB, et al; the AVID Investigators. *J Am Coll Cardiol*. 2003;42:81-87.

Mitchell and colleagues examined the association between therapy with lipid-lowering drugs and recurrent arrhythmias in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Patients in AVID had a history of either a cardiac arrest or sustained, symptomatic ventricular tachycardia (VT). Patients were randomized to therapy with either an implantable cardioverter defibrillator (ICD) or an antiarrhythmic drug. In the substudy reported here, correlations between the use of lipid-lowering therapy and arrhythmias documented by ICD interrogation in the ICD group who had coronary artery disease and who survived at least 1 month after randomization were examined.

Lipid-lowering drugs were prescribed at the discretion of the patient's primary physician. Use of lipid-lowering therapy was then incorporated into a Cox proportional hazards model that included other factors previously reported to be predictors of outcome in this study. These factors include: presenting arrhythmia (VT or ventricular fibrillation [VF]), history of cerebrovascular disease, left ventricular ejection fraction, history of other arrhythmias, and absence of revascularization during the index hospitalization.

The cohort for this analysis included 362 patients—279 (77%) patients who did not receive lipid-lowering therapy and 83 who did. Patients who did not receive lipid-lowering therapy were slightly older (67 ± 10 years vs 64 ± 10 years), less likely to be male or white, and more likely to have had VT compared to VF.

ICD patients who received lipid-lowering therapy had improved survival free of VT/VF compared to those not on therapy. After adjustment for baseline inequalities, there was a reduction in relative hazard for VT/VF recurrence of 0.40 (95% CI, 0.15-0.58). A similar effect on all-cause mortality was seen with a relative hazard associated with lipid-lowering therapy of 0.36 (95% CI, 0.15-0.68).

Mitchell et al conclude that lipid-lowering therapy is associated with a decrease in recurrent VT/VF and improvements in all-cause and cardiac mortality.

COMMENT BY JOHN DiMARCO, MD, PhD

There are several interesting points we should take from this paper. First, the paper highlights a recent re-emphasis on triggering events as important factors in the causation of sudden death. In the 1980s, the emphasis had been on the fixed electrophysiologic substrate created by large scars, and sustained monomorphic tachycardia was thought to be the basic problem underlying most sudden deaths. However, over the last few years, it has been increasingly recognized that a complex interaction between triggers and this substrate initiates the ventricular arrhythmias that cause sudden death. Acute ischemia is one of these triggers. Lipid-lowering therapy may stabilize atherosclerotic plaques and prevent or decrease the frequency of severe ischemia, thus lowering the incidence of ventricular arrhythmias in susceptible individuals.

Other explanations should also be considered. Statins may have some direct effects on ionic channel that modulate repolarization. They may favorably affect ventricular remodeling that occurs after an infarction. These effects may be independent of the effect on serum lipids.

Attempts to decrease sudden death mortality by targeting specific ionic channels have been largely unsuccessful. We now should concentrate on interventions that, although less clearly related to electrophysiologic phenomena, have been shown to decrease sudden death in clinical trials. These interventions, which include beta blockers, ACE inhibitors, and lipid-lowering therapies, should be routinely employed with defibrillator therapy added for the highest-risk patients. One of the striking findings in this report is the relatively low proportion of patients in this trial who were on lipid-lowering therapy. ■

Pulmonary Vein Ablation for Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *The described technique for pulmonary vein ablation yields results superior to medical therapy in a broad spectrum of patients with atrial fibrillation.*

Source: Pappone C, et al. *J Am Coll Cardiol*. 2003;42:185-197.

Pappone and colleagues present an observational study evaluating the efficacy of their laboratory's

technique for pulmonary vein isolation. The approach used by Pappone et al involves circumferential isolation of the pulmonary vein ostia using an electroanatomic approach. This technique places a ring of lesions at least 5 mm from the ostia themselves. Pappone et al report on 1171 consecutive patients with paroxysmal or chronic atrial fibrillation referred to their laboratory for evaluation. Of these, 589 patients underwent pulmonary vein isolation and 582 received medical therapy. Therapy was selected by Pappone et al and was not randomly assigned. The entire group had a mean age of 65, and 59% were male. About 35% had no structural heart disease, and 44% had only hypertension. The mean left ventricular ejection fraction was 54%, and the mean left atrial diameter was 4.5 cm. The ablation group was then compared to the medical therapy group in terms of the following parameters: total mortality, nonfatal adverse cardiac events, atrial fibrillation recurrence, left atrial size change, hospitalization, and quality of life. The median follow-up was 900 days for both groups.

There were 38 (6%) deaths in the ablation group vs 83 (14%) deaths in the medical therapy group. Observed survival probabilities were 98%, 95%, and 92% at 1, 2, and 3 years, respectively, in the former group, and 96%, 90%, and 86% in the latter group. Survival in the ablation group matched expected survival for an age-matched Italian population. Survival was poorer than expected in the medical therapy group. Heart failure and ischemic strokes or transient ischemic attacks were more common in the medical group. In both groups, these adverse effects were usually associated with recurrent atrial fibrillation (72%) and/or inadequate anticoagulation (50%). Ablation was associated with improved rhythm control with 120/589 (20%) ablation patients compared to 340/582 (58%) medical therapy patients experiencing 1 or more recurrences of atrial fibrillation. The majority of the ablation patients who developed recurrent atrial fibrillation did so during the first year after their procedure. An enlarged (> 4.5 cm) left atrium and a smaller area encircled by the ablation lesions were predictors of recurrence. There was also a fourfold reduction in left atrial size and an increase in peak A-wave velocity in the ablation group. Finally, the ablation group, but not the medical group, reported an improvement in quality of life. Medical therapy patients reported no change in quality of life during the course of the study.

Pappone et al conclude that their technique for pulmonary vein ablation yields results superior to medical therapy in a broad spectrum of patients with atrial fibrillation.

■ **COMMENT BY JOHN DiMARCO, MD, PhD**

Since the initial description of focal sources of atrial fibrillation arising from the pulmonary veins, there has been intense interest in catheter ablation as a potential cure for atrial fibrillation. As yet, there has not evolved a standard approach for either selecting patients or actually performing the procedure.

Pappone et al present the first truly large series of patients who have undergone pulmonary vein ablation. The group was predominantly middle-aged, and many patients had a history of hypertension, the most common etiology of atrial fibrillation in this age group. Although there were relatively few patients with severe left ventricular dysfunction, this patient group is more representative of the average atrial fibrillation patient than has been reported in other ablation series, which often had a large proportion of young patients with no heart disease. In these patients, Pappone et al report excellent success rates and virtually no acute or long-term complications.

The technique used by Pappone et al is somewhat different from that used in most laboratories. The ablation lesions are placed anatomically in rings around the pulmonary vein ostia. These large rings also include a portion of the posterior left atrial wall, and this may contribute to the high efficacy rate reported here. Since detailed mapping is not performed, less instrumentation is required and the procedure duration is comparatively short.

The major limitation of this paper is that the assignment of ablation or medical therapy was not randomized. Most patients in both groups had previously had recurrences while on drugs, so recurrent arrhythmias should not have been unexpected. Amiodarone, the most effective antiarrhythmic drug, was used in only 33% of the medical therapy patients. Factors not included or completely accounted for by the Cox proportional hazards model likely affected outcomes. The data here do not imply that ablation should be first-line therapy. Rather, they imply that ablation is an evolving strategy that provides an alternative to drug therapy for an expanding pool of patients. ■

New Aspects of Atherosclerotic Plaque Biology

ABSTRACTS & COMMENTARIES

Sources: Dechend R, et al. *Circulation*. 2003;108: 261-265; Sano T, et al. *Circulation*. 2003;108:282-285.

In the Dechend study, German investigators examined the role of *Chlamydia pneumoniae* (CP) in

the atherosclerotic inflammatory process, based on previous studies indicating that this organism can be cultured from coronary atheromata. This group had previously demonstrated that CP-infected vascular smooth muscle cells (VSMC) can activate various nuclear transcription factors in target genes, leading to enhanced thrombogenicity and cytokine production. They have also shown that statins favorably modify this process. In the present study, they demonstrate that human macrophages infected with CP are able to transmit the infection to VSMC and that processes modulated by the HMG CoA reductase enzyme induce CP-stimulated cellular interactions and activation. Statins were shown to reduce the risk of CP infection of VSMC; reduce the production of IL-6 and PAI-1 expression; and reduce activation of membrane-bound compounds, such as RAC1 and RhoA, all of which could be reversed by mevalonate. Furthermore, NF-kb activation was observed following CP infection and was reduced by statins in a dose-dependent fashion; this was also blocked by mevalonate. Other cellular phenomena, involving RANTES and MCP-1, were activated in infected macrophages and VSMC; this was also decreased by statins. Induction of IL-6 and IL-8 similarly was favorably modulated by statins. Reactive oxygen species were diminished by statins and in infected VSMC, RHO, and RAC prenylation were inhibited by statins.

Dechend and associates believe that monocytes and macrophages may harbor CP in a persistent state not amenable to antibiotic treatment. The infection can be spread through involvement of VSMC, confirming immunomodulatory cross talk between the infected and noninfected cells. They state that "statins may decrease not only the chain of events leading to inflammation and activation in infected VSMC but also their propensity to become infected." Proliferation and secretion of IL-2 and other cytokines within the atherosclerotic plaque was stimulated by CP infection. The atherosclerotic lesion contains inflammatory CD-4 T cells and macrophages; T cells are activated and secrete cytokines. Only human cells were used in this study and the CP strain used was isolated from a human plaque; thus, it would appear that the results are germane to humans. Statins appear to interrupt the vicious cycle stimulated by CP infection and the subsequent activation of inflammatory cytokines and NF-kB.

COMMENT BY JONATHAN ABRAMS, MD

These in vitro data, while somewhat difficult for the uninitiated to follow the intracellular molecular pathways, clearly suggest that CP infection may potentiate activation of atherosclerotic plaques and demonstrate that statins can reduce macrophage-mediated CP signaling and transmission. This presumably represents a nonlipid or pleiotropic benefit of the HMG CoA reductase inhibitors. The study further supports the hypothesis that chronic CP infection can potentiate adverse vascular events by immunomodulation of a variety of phenomena within the plaque. Inflammatory cells, reactive oxygen species, cytokines, and chymokines are all involved in these processes. Thus, CP may not only contribute to inflammation leading to atherothrombosis but may also make the plaque more vulnerable to rupture. Statins in this model were impressively effective in blocking a variety of adverse intracellular pathways. The fact that mevalonate can, in turn, block the effects of statins indicates that products of HMG CoA reductase inhibition other than decreasing cholesterol production occur with statins and are important nonlipid moieties, confirming pleiotropic effects of this drug.

Plaque Rupture

A separate study by Sano and colleagues focusing on plaque rupture using intravascular ultrasound (IVUS) comes from Japan and suggests that C-reactive protein (CRP) activation may contribute to the identification of plaques at high risk for rupture in patients with acute myocardial infarction (AMI). Sano et al performed coronary angiography on 90 consecutive ST elevation AMI within 6 hours of symptoms. Subjects were divided into a normal and elevated CRP group (> 3 mg/dL). There were no clinical features differentiating the 2 groups, which consisted of 43 and 47 patients, respectively. Serum markers and angiographic findings were identical. However, the high CRP group was associated with a higher rate of plaque rupture, with fissuring and dissection in 56% of the entire group; this phenonoma was more frequent in the elevated CRP cohort (58% vs 34%; $P = .03$). After multivariate logistic regression adjustment, "the presence of ruptured plaque alone correlated with elevated serum CRP." Sano et al point out that CRP may be synthesized following the acute stimulus of myocardial necrosis. The elevated CRP in such patients is speculated to reflect the status of the coronary lesion just before rupture as opposed to reflecting myocardial necrosis. Furthermore, Sano et al suggest that high CRP reflects the activity of activated macrophages, which are capable of degradation of extracellular matrix and secretion of proteolytic enzymes predisposing to plaque rupture. CRP has been associated with "active" angina, and it has been suggested that high CRP may predict the future risk of AMI. Recent data suggest that CRP may be a player,

not just a marker, in promoting vascular inflammation and plaque destruction. In normal CRP patients, 44% had nonrupture lesions, and many were due to plaque erosion; such lesions may have a less robust inflammatory response. Sano et al conclude that these data should be taken into account when performing percutaneous coronary interventions (PCI), as prior studies have indicated that CRP is a marker for adverse outcomes in this setting, possibly associated with the no reflow phenomenon or acute occlusion after angioplasty. Sano et al have described a lipid pool-like image on IVUS that is common in the plaque rupture group, which may be a marker for less-than-optimal PCI results.

COMMENT BY JONATHAN ABRAMS, MD

The use of CRP measurements in acute coronary syndromes (ACS) or acute ST elevation AMI (STEMI) has not reached the clinical arena as yet, nor should it. Nevertheless, there are increasing data that this inflammatory marker, if elevated, is a predictor of adverse outcomes and, as this study suggests, may have some correlation with plaque rupture. There was a 70% incidence of rupture in the 43 high CRP individuals compared to 34% in the normal CRP individuals. As Sano et al point out, there may be some false negatives through the use of IVUS, but, nevertheless, the data are intriguing, particularly the increased presence of the lipid pool-like image on IVUS that occurred in half of the high CRP patients and only 30% of the normal CRP group. It must be kept in mind that these patients all had ST elevation MI, and the data may not be predictive of elevated CRP in individuals with ACS or a non-STEMI. It is likely that CRP levels will become part of the routine AMI and ACS lab package in the near future, although at the present time there are no definite interventions that can be recommended over and above the present pharmacological cocktails for these patients. The interested reader is referred to an editorial in the same issue of *Circulation* titled, "The Future of Biomarkers In Acute Coronary Syndromes. Moving Towards a Multi-Marker Strategy," by Morrow and Braunwald, which impressively lays out the case that future practice is likely to include routine measurements of a number of biomarkers, including creatinine clearance, BNP or NT-proBNP, high sensitivity CRP, CD40, ligand, and troponin.[1] It seems that a "heart attack" is no longer a simple event! ■

Reference

1. Marrow DA, Braunwald E. *Circulation*. 2003;108: 250-252.

CME Questions

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13. Severity of mitral regurgitation is best established by:
a. color jet characteristics.
b. mitral and pulmonary vein inflow.
c. quantitation of regurgitant flow.
d. integration of several techniques.

14. Mitral valve repair for regurgitation is most beneficial in patients:
a. younger than 60 years old.
b. with CAD.
c. with LV dysfunction.
d. with rheumatic valve disease.

15. Low gradient aortic stenosis is characterized by:
a. valve area < 1.0 cm^2.
b. mean gradient < 40 mm Hg.
c. low cardiac output.
d. All of the above

16. Statins have which of the following effects?
a. Reduce LDL-cholesterol levels
b. Reduce inflammation
c. Reduce ventricular arrhythmias
d. All of the above

17. Radiofrequency catheter ablation is being applied increasingly to:
a. recurrent ventricular fibrillation.
b. atrial fibrillation.
c. inappropriate sinus tachycardia.
d. Brugada's syndrome.

Answers: 13(d); 14(a); 15(d); 16(d); 17(b)

Readers are Invited. . .

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