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Prevention of Postoperative Atrial Fibrillation

ABSTRACT & COMMENTARY

Crystal and colleagues report a meta-analysis on the effects of pharmacologic or pacing therapy for the prevention of postoperative atrial fibrillation (AF) in patients undergoing heart surgery. Studies were included if they met all of the following criteria: randomized controlled trials of intervention vs. placebo or usual care; primary prevention of postoperative AF after coronary artery bypass surgery; treatment started immediately before, during the operation, or within the postoperative intensive care unit; a well-described intervention protocol; and adequate data on treatment efficacy. The primary outcome measure used for the meta-analysis was the incidence of postoperative AF or atrial flutter. Secondary outcome measures that were analyzed for selected studies were length of stay and the incidence of stroke.

There were 42 trials that evaluated the effects of beta-adrenergic blockers, sotalol or amiodarone, included in this series. The studies ranged between 36 and 1000 patients in size.

There were 27 trials that evaluated a beta blocker for prevention of postoperative AF. These trials included 3840 patients. In these trials, the AF incidence was 33% in the control group vs. 19% in the beta blocker group (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.28-0.52). The test for heterogeneity in these trials was highly significant at $P = 0.00001$, and the reason for this was not explained. The test for overall effect was highly significant ($P < 0.00001$).

Eight trials were analyzed that evaluated the use of sotalol. These studies included 1294 patients. Sotalol reduced the incidence of AF from 37% in the control group to 17% in the treatment group (OR, 0.35; 95% CI, 0.26-0.49). There was no significant heterogeneity between the trials.

Nine trials evaluated the use of amiodarone. These trials included 1384 patients. Amiodarone reduced the incidence of AF from 37% in the control group to 22.5% in the amiodarone group (OR, 0.48; 95% CI, 0.37-0.61). There were 4 trials that compared sotalol and other beta blockers. These trials included 900 patients. Sotalol was

Volume 21 • Number 9 • September 2002 • Pages 65-72

INSIDE

associated with a decreased incidence of AF—22% vs. 12% (OR, 0.50; 95% CI, 0.34-0.74).

The effects of pacing on the incidence of postoperative AF were also examined. There were 10 trials that involved either right atrial pacing, left atrial pacing, or biatrial pacing. There was no standardization in the pacing algorithm used. Right atrial pacing was associated with an OR of 0.68 (95% CI, 0.39-1.19). Left atrial pacing was associated with an OR of 0.57 (95% CI, 0.28-1.16). Biatrial pacing was associated with an OR of 0.46 (95% CI, 0.30-0.71).

The effects of intervention on length of stay were reported by 2 beta blocker trials, 5 sotalol trials, and 5 amiodarone trials. Beta blockers and sotalol were associated with nonsignificant trends toward shortening of length of stay. Amiodarone reduced length of stay significantly by 0.91 days (95% CI, 1.59-0.24 days). Biatrial pacing also significantly reduced the length of stay.

The incidence of stroke was available only in 14 of the 52 trials, which covered 2877 patients. In these trials, the percentage of patients who developed AF was reduced from 38.6% in the control group to 23.7% in the treatment group. Despite this reduction, the incidence of stroke was 1.2% in the treatment group and 1.4% in the control group (OR, 0.90; 95% CI, 0.46-1.74). Crystal et al conclude that beta blockers, sotalol, and amiodarone are all effective for the prevention of postoperative atrial fibrillation. They recommend that beta blockers should be the first-line medication, with sotalol and amiodarone as appropriate alternatives (Crystal E, et al. *Circulation*. 2002;106:75-80).

■ COMMENT BY JOHN P. DiMARCO, MD, PhD

Postoperative AF remains a frustrating problem for cardiologists and cardiovascular surgeons. In patients without a prior history of AF, postoperative AF usually occurs between the second and sixth postoperative day and usually will resolve within the first 2-4 weeks after the operation. As noted in this review, strategies to prevent postoperative AF have included beta blocker therapy, antiarrhythmic drugs, and pacing strategies.

The data here show that beta blockers remain the mainstay of the strategy for reducing the incidence of postoperative AF. Therapy with beta blockers is inexpensive, well tolerated, and easy to initiate. More powerful antiarrhythmic drugs or pacing strategies should be considered either in conjunction with beta blockers if beta blockers have failed or if there is a very high preoperative probability for developing AF. Patients with a prior history of AF or mitral valve disease would be candidates for a more aggressive approach.

It should be noted however that none of these strategies eliminate postoperative AF. The next step in trials might be a combination of beta blockers with either pacing or amiodarone to see if that would further reduce the incidence. It should also be remembered that left atrial radiofrequency lesions placed at the time of surgery could eliminate late AF in many patients. This latter procedure is becoming more widespread in patients undergoing mitral valve surgery. ■

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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1 year *with* Free AMA Category 1 credits: $287
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Multiple Copies
2-9 additional copies: $213 each. 10 or more copies: $190 each.
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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis. Dr. DiMarco does research for Medtronic, Guidant/CPI, Pfizer, Bayer, and Wyeth-Ayerst. Drs. Crawford and Vernon report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Predictive Value of Coronary Pressure Measurements After Stenting

ABSTRACT & COMMENTARY

Synopsis: This registry analysis demonstrates that FFR after stent implantation has strong, independent predictive value with respect to clinical outcomes at 6 months.

Source: Pijls NHJ, et al. *Circulation*. 2002;105: 2950-2954.

The presence of a significant pressure gradient within a coronary artery during maximal coronary

blood flow suggests the presence of inadequate coronary flow reserve, and hence, a functionally significant coronary obstruction. Determination of fractional flow reserve (FFR) using a pressure-sensing guidewire and induction of coronary hyperemia induced by a microcirculatory vasodilator such as adenosine is a useful and convenient method for evaluating the physiologic significance of a coronary stenosis in the cardiac catheterization laboratory. FFR is the ratio of the mean distal coronary pressure (P_d) measured by the pressure wire placed beyond a coronary stenosis, to the mean proximal coronary pressure (P_a) at the tip on the guiding catheter. FFR can be used to evaluate the functional significance of an angiographically intermediate lesion, with FFR < 0.75 showing good correlation with ischemia documented by perfusion imaging and FFR > 0.75 correlating with low event rates at 1 year. FFR has also been shown to be a useful alternative to intravascular ultrasound (IVUS) for assessing the adequacy of stent implantation. However, the use of FFR measurement in assessing or improving clinical outcomes after stent implantation has not been described.

Pijls and colleagues present a retrospective analysis of data obtained from the Fractional Flow Reserve (FFR) Post-Stent Registry. They sought to determine whether post-stent implantation FFR correlated with clinical outcomes, using the end point of major adverse cardiac events (MACE), including death, myocardial infarction (MI), or target vessel revascularization (TVR) during 6 months of follow-up. The study population included patients from 15 hospitals who underwent coronary stenting in which a pressure wire (Radi Medical Systems—Uppsala, Sweden) was used as a guidewire for any reason. The stent implantation procedures (including use of adjuvant medical therapy) were performed at the operator's discretion per local routine. After each angiographically successful stent procedure (< 10% residual diameter stenosis by visual estimation), FFR was determined during peak hyperemia induced by intracoronary administration of adenosine, ATP or papaverine, or by intravenous administration of adenosine or ATP. Data were analyzed using FFR as a dichotomous variable (FFR > 0.95 vs ≤ 0.95, or FFR > 0.90 vs ≤ 0.90) and as a continuous variable divided into 5 groups (0.75-0.80, 0.81-0.85, 0.86-0.90, 0.91-0.95, and 0.96-1.0).

The registry included 750 patients and 6-month follow-up was complete in 744 patients (99.2%). Baseline characteristics demonstrated that this patient population was similar to the average PCI populations from other large studies. On average, 1.18 stents were used per patient, with a stented length of 17.3 ± 6.4 mm. Final FFR > 0.95 was achieved in 68%, and FFR > 0.90 was achieved in 68% of patients. Final FFR was < 0.75 in 11 patients (1.5%) suggesting that these stent procedures were "physiologically unsuccessful." During the 6 months of follow-up, 90 events occurred in 76 patients and included 5 deaths (0.7%), 19 MIs (2.6%), 12 bypass graft surgeries (1.6%), and 54 PCIs (7.3%). By univariate analysis, significant predictors of adverse events were final FFR ($P < 0.01$), smaller stent diameter ($P = 0.023$), and longer stent length ($P = 0.032$). When the data were analyzed using 5 categories for FFR, there was a significant inverse correlation between final FFR and total MACE ($P \leq 0.001$), as well as death or MI ($P < 0.01$), and TVR ($P < 0.001$). Patients in the highest category (FFR = 0.95) had the lowest event rate (4.9%) and patients in the lowest category (FFR < 0.80) had the highest adverse event rate (28.5%). Using multivariate analysis, only final FFR category ($P < 0.001$) and length of stent ($P < 0.01$) were predictive of adverse events.

Pijls et al conclude that this registry analysis demonstrates that FFR after stent implantation has strong, independent predictive value with respect to clinical outcomes at 6 months. In their discussion, they describe potential explanations for the correlation between FFR and clinical outcomes. Lower postprocedural FFR might reflect inadequate stent expansion, abnormal residual shear stress, or significant disease in the unstented portions of the target vessel, all of which could contribute to a persistent hyperemic pressure gradient. Based on their previous work, Pijls et al stress the importance of truly maximal hyperemia in performing accurate FFR measurements, recommending intracoronary adenosine doses of ≥ 30 mg for the right coronary artery and ≥ 40 mg for the left coronary artery. They point out that while abnormal FFR is indicative of a suboptimal procedural result, it does not elucidate the mechanism of the problem, which might be revealed by IVUS examination. They acknowledge the limitations inherent in this registry analysis and suggest that a prospective study to determine whether additional intervention can improve a suboptimal FFR and improve patient outcomes would be useful.

COMMENT BY SARAH M. VERNON, MD

In recent years, the interventionalist's armamentarium has expanded to included an array of different stent designs and sizes on markedly improved delivery systems. In addition to allowing the operator to tackle increasing complex lesions and anatomy with good outcomes, this equipment has made the straightforward lesion a "slam-dunk" for the experienced interventionalist. In the interest of time and expense, these lesions can be treated using direct stenting (without predilitation),

moderate pressure deployment (though most available stents are mounted on compliant or semi-compliant balloon delivery systems), and in some cases, without high pressure postdilitation (saving the expense of an additional balloon). These procedures are quick and easy, and often give an "occulostenotically" satisfying result (0% residual stenosis, TIMI 3 flow), at least angiographically. However, the question for each individual patient remains: Is this result as good as it can be? Or even good enough?

Postdeployment evaluation of a stented artery using IVUS can be a very enlightening (and sometimes sobering) experience. Results can look much less optimal (undersized or incompletely expanded stents, residual uncovered disease) when viewed from the inside out. However, in most cath labs, IVUS evaluation adds considerable time and expense to the procedure. The imaging catheters and equipment are expensive and good data interpretation takes considerable expertise. By contrast, physiologic evaluation using a pressure wire system is remarkably quick and easy to perform. In our laboratory, a pressure wire evaluation (we use the Endosonics system) adds only minutes to the procedure and can provide important diagnostic information (Is this lesion really tight? Which of these lesions is the "culprit"?), in addition to important feedback about the physiologic result when a PCI procedure is undertaken. The wires are easy to manipulate, the measurements are quick and extremely easy to make (the FFR is read from a console), and the procedure is extremely well tolerated by patients (even when high-dose intracoronary adenosine is given). When a PCI is deemed to be physiologically appropriate, the pressure wire can then be used as the guidewire for the intervention (if rota is not performed) and remains in place until the postprocedural physiologic assessment is complete.

Pijls et al provide data suggesting that an optimal physiologic result, as measured by postprocedural FFR, should be more important to the interventional operator (and to his or her patient) than another pretty picture. The pressure wire might tell us that our "slam-dunk" procedure is, in fact, not quite finished. A low FFR might suggest that perhaps this patient's clinical outcome could be improved by a high-pressure postdilitation, or by looking to see what the problem is using IVUS, for example. This paper tells us that careful evaluation and optimization of our "physiologic" results might make a real difference for our patients. While the availability of coated stents is just around the corner, the revolution they herald will be incomplete if we lose sight of how to optimally deploy them. ■

Reliability of Doppler Echo for Valvular Regurgitation

ABSTRACT & COMMENTARY

Synopsis: Interstudy variability was substantial for the color Doppler assessment of the severity of AR and MR and were related to changes in blood pressure and regression to the mean.

Source: Gottdiener JS, et al. *Am Heart J*. 2002;144: 115-121.

Color doppler echocardiography is the principle method for the serial evaluation of patients with left heart valve regurgitation, yet substantial variability in the estimated severity of regurgitation has been demonstrated. Thus, Gottdiener and associates sought to determine the relative contribution of acquisition vs. reader variability in the serial assessment of aortic regurgitation (AR) and mitral valve regurgitation (MR). The 23 subjects enrolled in the study ranged in age from 18 to 65 years and all had a body mass index > 27 kg/m^2 since they were derived from the control group of an obesity pharmacologic study. The subjects were selected for an even distribution of aortic and mitral regurgitation from none to severe. Using the same machine, the same sonographer performed 2 echoes 14 days apart and then a different sonographer repeated the second echo within 2 hours (third echo). Mitral regurgitation was graded as none, trace, mild, moderate, or severe using the color flow jet area to left atrial area ratio method. Aortic regurgitation was graded using the ratio of height of the regurgitant jet to left ventricular outflow tract area. All echoes were read by 2 blinded experienced readers in a random sequence and 9 were read twice by the same reader. Acquisition variability was determined as the total variability minus the intrareader variability. Blood pressure at the time of the echo was measured and showed considerable variability between studies. Total variability was 29% for AR and 25% for MR. Intrareader variability was 6% for AR and 17% for MR. Acquisition variability was 29% for AR and 8% for MR. Predictors of total variability included initial regurgitation grade; the higher the initial severity the more likely severity would decrease on the second exam and vice versa. Also, diastolic blood pressure was directly related to changes in severity of both MR and AR. Gottdiener et al concluded that interstudy variability was substantial for the color Doppler assessment of the severity of AR and MR and were related to changes in blood pressure and regression to the mean.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Changes in valvular regurgitation severity are important for assessing the response to specific therapy such as vasodilators, determining the timing of corrective surgery and evaluating changes in patient symptoms. Despite the importance of such decisions, the common use of color Doppler echo techniques to assess regurgitation severity are known to be problematic. The cardiology literature is filled with studies of new ways to assess regurgitation severity, each more complicated and problematic than the next. This has prompted some leaders in the field to recommend multi-measurement assessment systems, but the time required to do all the required measurements in the usual clinical practice makes this approach impractical. So most labs use the techniques studied in this report; jet area for MR and jet height for AR.

Considering that this was a research study performed under carefully controlled circumstances, the variability observed was considerable; 29% for AR and 25% for MR. The components of this variability was somewhat different for the 2 lesions. Echo acquisition issues were more prevalent with AR, including biological variability, mainly in blood pressure. Whereas, with MR, intrareader variability was more of a problem with considerable regression to the mean observed. The latter phenomena have been well studied and validated. Basically if a measurement is erroneous, a repeat measurement is unlikely to be more erroneous, so there is a shift toward the mean value. In the case of valve regurgitation severity this could be interpreted as a biologic change. Although not studied here, interreader variability is likely to be greater than intrareader. Thus, if this study was done under the usual clinical situation of different machines, sonographers, and readers, the results would probably have been worse. Clearly we need to do a better job reading serial studies in patients with valvular regurgitation.

This study has several limitations. The number of subjects is small. The technicians knew this study was focusing on MR and AR. Only 1 method of assessing regurgitation severity was used for each valve. Also, most of the subjects had trace-to-mild regurgitation. Several conclusions can be drawn, however, as pointed out by Dr. Schiller in his editorial. First, blood pressure should be measured and considered in the interpretation of the echo. Second, multiple methods of severity estimation should be used whenever possible. Third, changes in the trace-to-mild range should be downplayed. In my experience there is little difference between 1-2+ regurgitation (scale of 4 being severe). Finally, clinical decisions should take into account whether there are corresponding changes in LV and LA volume, LV function, estimates of filling pressure, and pulmonary artery pressure. Changes in 1 echo Doppler parameter alone are usually not sufficient to make major therapeutic changes. ■

Sudden Death After Radiofrequency Ablation of the Atrioventricular Node

ABSTRACT & COMMENTARY

Synopsis: The incidence of sudden death related to AV junctional ablation is low, but Ozcan et al recommend that in-hospital monitoring for a minimum of 2 days after ablation should be considered for patients with predictors of increased risk.

Source: Ozcan C, et al. *J Am Coll Cardiol*. 2002;40: 105-110.

This paper details the mayo clinic experience with unexpected sudden death after radiofrequency ablation of atrioventricular (AV) nodal conduction. All patients who underwent radiofrequency ablation of the AV node for paroxysmal or chronic atrial fibrillation (AF) at the Mayo Clinic between July 1990 and December 1998 were included in this series. Sudden death was defined as either witnessed death or death within 1 hour from the time the patient was last seen. The sudden deaths were classified as either likely, possibly, or unlikely to be related to the procedure. If sudden death occurred within 48 hours after the procedure or occurred at any time after the procedure in the presense of known coronary vascular disease, the relationship was defined as likely. Sudden deaths occurring in the interval between 2 days and 3 months after the procedure were defined as possibly related. Deaths that occurred more than 3 months after the procedure were defined as unlikely to be related to the procedure. Data were collected from a centralized data repository that provided complete records of patients who underwent AV node ablation and pacemaker implantation at the Mayo Clinic. AV node ablation was performed using a right-sided approach in 98% and a left-sided approach in 2%. Twenty- four patients (7%) developed recurrent AV conduction after an initial attempt and required a second or third procedure. AV block was eventually achieved in all patients. Patients in AF received a VVIR pacemaker. Patients with paroxysmal AF or those in sinus rhythm at the time of the procedure received a

dual chamber pacemaker. Before 1997, the lower pacing rate was programmed at 60 bpm. Since 1997, the lower pacing rate was set at 90 bpm immediately after ablation and decreased by 10 bpm per month to a final setting of 60 bpm.

The study included data from 334 patients. The mean age of patients in the study group was 68 ± 11 years. Nine patients had either sudden death (7) or aborted cardiac arrest after the ablation. In 3 patients, the sudden death was thought to be likely related to the procedure because the event occurred within 48 hours of the procedure in 3 cases, and 1 patient without any cardiovascular disease had sudden death 4 days after the procedure. Sudden death in 3 patients was classified as possibly related to the procedure because it occurred between 2 days and 3 months after the procedure. These 3 patients all had significant cardiovascular disease. Two patients died suddenly at 27 and 43 months after the procedure. Both had underlying structural heart disease, and their deaths were considered to be unlikely to be related to the procedure. Among the patients with sudden death likely or possibly related to the procedure, 6 of the 7 patients had structural heart disease. Ventricular arrhythmia had been noted before the procedure in 4 of the 7 patients. Six of the 7 patients had AF at the time of ablation. Six of the 7 patients had a lower pacing rate programmed at 60 bpm immediately after the ablation, with only 1 having the higher pacing rate. The following were identified as independent predictors for sudden death: diabetes mellitus, New York Heart Association functional class ≥ 2, preablation ventricular arrhythmias, valvular heart disease (mitral stenosis, aortic stenosis, aortic regurgitation), and chronic lung disease. Five of the arrests occurred in the hospital during postprocedure monitoring. Ventricular fibrillation was noted in 4 patients and polymorphic ventricular tachycardia in 1 patient. There was no evidence for pacemaker failure or malfunction in any of the patients. Ozcan and colleagues conclude that the incidence of sudden death related to AV junctional ablation is low but recommend that in-hospital monitoring for a minimum of 2 days after ablation should be considered for patients with predictors of increased risk.

COMMENT BY JOHN P. DiMARCO, MD, PhD

AV junctional ablation was first performed using direct current shocks. This produced a relatively large lesion and there was a significant early and late morbidity and mortality associated with the procedure. The development of radiofrequency techniques allowed more precise localization and control of the lesion used for elimination of AV node conduction, and it was hoped that this would lower the risk of ventricular arrhythmias after the procedure. This paper from a single center covers a large number of patients who were treated using a uniform approach. Ozcan et al document a low incidence of sudden death or cardiac arrest that was considered to be likely related to the procedure, and these data can be used to formulate practical guidelines.

The mechanisms responsible for sudden death in these patients are uncertain. The late sudden deaths are probably related to the progression of the patient's underlying disease. There was no evidence in this series of pacemaker failure. Even if the pacemaker failed, most patients who have undergone AV junctional ablation will have an escape rhythm adequate to support life long enough for the patient to get to the hospital. It has recently been thought that bradycardia-dependent arrhythmias due to the sudden change in rate might be responsible. For this reason, most electrophysiologists now pace the heart at a lower rate limit of 80-90 bpm for some period of time after the procedure. It should be noted in this series that only one of the patients with sudden death or cardiac arrest were paced at the higher rate and that this laboratory changed their protocol to the higher lower rate limit several years ago. The single patient after the change in protocol had a cardiac arrest 13 days after the procedure and had significant left ventricular dysfunction before the procedure.

The risk factors identified for sudden death in this trial are important for clinicians. Heart rates during AF are often very difficult to control in patients with progressive valve disease or chronic obstructive lung disease. It seems fully justified to keep these patients in the hospital for more than 24 hours based on these data. The observation that diabetes was an independent predictor for sudden death is intriguing. Whether this is related to repolarization abnormalities or antihyperglycemic agents or whether the diabetes was just a marker for underlying coronary artery disease is uncertain.

I think electrophysiologists should follow the suggestions made by Ozcan et al based on their data. Patients with any of the risk factors identified should be monitored at least 48 hours in the hospital. The pacing rate after the procedure should be higher than was used in the early part of this series. Even if the sudden death rate after AV junctional ablation is low, we must remember to be cautious in managing these patients around the time of the procedure. ■

Hot Plaques in Acute Coronary Syndromes?

ABSTRACT & COMMENTARY

Synopsis: Systemic anti-inflammatory therapy may be superior to focal angioplasty for preventing future coronary events in patients with unstable angina.

Source: Buffon A, et al. *N Engl J Med*. 2002;347:5-12.

For much of the last decade, dr. a. maseri's group in Rome, Italy, have been exploring the hypothesis that acute coronary disease is related to an inflammatory process. Beginning in 1994, with multiple subsequent publications since, they have demonstrated activation of the coronary bed with increased leukocyte CD11b and CD18; activated monocytes and neutrophils; cytokine elevations; and increases in the metalloproteinase and collagenases. Other workers have corroborated their data. In an intriguing report from William Beaumont Hospital 2 years ago (Goldstein J, et al. *N Engl J Med*. 2000;343:2115-2122), it was demonstrated that patients with acute myocardial infarction (MI) frequently had multiple complex coronary lesions in coronary vessels not involved with the infarction itself, suggesting widespread activation of the coronary tree. In the present study, Maseri et al used an intricate protocol involving measurements of white blood cell and neutrophil myeloperoxidase (NM) content in the coronary arteries and the cardiac and femoral venous circulations in 5 different patient groups to determine whether there is widespread vs. localized inflammation in the coronary arterial bed during episodes of unstable angina pectoris. During cardiac catheterization, catheters were placed in the right femoral vein, aorta, great cardiac vein, as well as in the right and left anterior descending coronary arteries. Simultaneous sampling was obtained from all sites for NM concentration analyzed by automated flow cytochemistry. A low NM index indicates neutrophils that are depleted of myelperoxidase due to activation; a zero or positive index is consistent with nonactivation. If the index is low in the great cardiac and femoral veins compared to the aorta, this supports neutrophil activation across the coronary bed. C-reactive protein was measured in all subjects. The left and right coronary circulations were evaluated for the presence of plaque. The patient cohorts included 24 subjects with unstable angina and LAD stenosis and 9 with an RCA stenosis; 13 individuals with chronic stable angina; 13 with variant angina and recurrent ischemia; and 6 controls. The great cardiac vein drainage comes from the LAD but not the RCA, allowing assessment of localized neutrophil activation. Sampling from the femoral vein allowed the assessment of more generalized neutrophil activation in patients with unstable or variant angina who had typical clinical symptoms.

Results

The leukocyte and neutrophil counts in the aorta, great cardiac vein, and femoral vein were similar among all 5 groups. RCA lesions were associated with minimal LAD disease, whereas LAD unstable angina subjects had little to no RCA disease. Median aortic myeloperoxidase levels did not differ between patients with unstable angina who had left or right coronary lesions, but their NM levels were substantially lower than in individuals with stable angina, variant angina, or controls. There was a significant transcoronary decrease in the NM index only in the unstable angina patients. CRP levels were markedly elevated in the unstable angina group at 4.5- 6.5 mg/L, compared to 2.1 mg/L in stable angina subjects, 2 mg/L in patients with stable or variant angina, and 1.2 mg/L in controls. There was a significant negative correlation between systemic CRP levels and aortic and great cardiac vein NM concentration. Buffon and colleagues conclude that "leukocytes become activated as they traverse the coronary vascular bed" in unstable angina but not in variant or stable angina. Furthermore, transcoronary neutrophil activation was not found solely in the vascular bed perfused by a single decreased coronary artery but was found in both the right and left sides of the coronary circulation. Buffon et al speculate that "multifocal or widespread inflammatory activation of the endothelium" relates to a change in the "interface between the blood and the vessel walls from anticoagulant and vasodilative to prothrombotic and vasoconstrictive." Activation of metalloproteinase and collagenases are believed to be related to severe endothelial dysfunction and even lysis within the plaque capsule. Buffon et al cite a number of other reports that are consistent with widespread coronary inflammation in ACS, including autopsy analyses of Falk and Davies; postmortem plaque analyses demonstrating inflammatory-cell infiltrates with high content of proinflammatory cytokines; and studies of coronary flow and labeled deoxyglucose uptake in myocardial beds served by normal coronary arteries during unstable angina. Elevated CRP and interleukin-6 have been documented by Maseri et al's in more than two thirds of patients with severe unstable angina, declining somewhat by 6 months. Such levels are associated with unstable coronary plaque activation and an increase in subsequent clinical events, including MI. These findings are much less

common in individuals who present with an acute MI not preceded by unstable angina, suggesting that "triggers of coronary thrombosis and vasoconstriction are not necessary the same in all patients with ACS." Finally, Buffon et al conclude that their work challenges the well known hypothesis that a single activated or vulnerable plaque is "the genesis of coronary instability."

A companion editorial by Keaney and Vita discusses the implications of this study (Keaney JF, Vita JA. *N Engl J Med*. 2002;347:55-57). They emphasize the well-known fact that coronary angiography has not been very useful in identifying inflammed athroscoletic plaque, and that many acute coronary syndromes arise from non-stenotic vessels. They suggest that "systemic medical therapy is superior to focal angioplasty in preventing future coronary events in patients with unstable angina." They point out that considerable research is currently underway to try to identify unstable plaque and widespread coronary inflammation in a noninvasive fashion, which may result in new therapies with potentially enormous public health implications.

COMMENT BY JONATHAN ABRAMS, MD

The inflammation concept was advanced many years ago and was particularly emphasized in an early publication by the Rome group demonstrating increased CRP and serum amyloid A protein in severe unstable angina (*N Engl J Med*. 1994;331:317-324). The CRP story is now well known, with elevations documented in a wide variety of conditions. In both chronic and acute coronary syndromes, high CRP is associated with adverse short- and long-term prognosis. This is completely consistent with the inflammatory hypothesis. In the report from Goldstein et al, multiple complex plaques were found in coronary arteries away from the culprit lesion, suggesting an activated vascular state. Angioplasty with or without stenting is obviously not a "complete" therapy in such a situation. A variety of laboratories, including those of Libby, Ridker, and others, indicate that inflammation is tightly linked to atherosclerosis as well as to instability of atherosclerotic plaque. Many imaging techniques are currently being evaluated, including plaque thermography assays of multiple markers of inflammation, intravascular ultrasound, and MRI. It is widely believed that statin therapy plays a role in quenching coronary inflammation, and these drugs may work in part due to the nonlipid effects. Furthermore, the substantial benefits of aspirin in unstable coronary syndromes may be linked to the inflammatory hypothesis. Measurements of CRP are not advocated at the present time, but it is likely that, in the near future, widespread use of high sensitivity-CRP levels and perhaps other cytokines will be part of the evaluation of acute coronary syndromes to determine the presence and degree of inflammation. In spite of all this exciting research, the precise causes of the inflammatory stimuli are yet to be determined. ■

CME Questions

12. Post heart surgery atrial fibrillation can be effectively prevented by:
a. sotolol.
b. amiodarone.
c. beta blockers.
d. All of the above

13. Sudden death after radiofrequency AV node ablation occurs in:
a. 2%.
b. 10%.
c. 15%.
d. 20%.

14. Poststent Doppler wire assessment of fractional flow reserve:
a. adds considerable time and cost to the procedure.
b. is superior to IVUS evaluation.
c. predicts 6 month adverse clinical outcomes.
d. may dislodge the stent.

15. Coronary inflammation markers suggest:
a. activity of a culprit lesion.
b. widespread coronary endothelial inflammation.
c. stable angina.
d. variant angina.

16. The variability of echo Doppler assessment of valve regurgitation severity is:
a. low.
b. better for MR vs. AR.
c. related to changes in blood pressure.
d. All of the above

Attention Readers . . .

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com.

We look forward to hearing from you. ■