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# CLINICAL CARDIOLOGY ALERT

*A monthly update of developments in cardiovascular disease*

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## INSIDE



# Does Diastolic Heart Failure Really Exist?

ABSTRACT & COMMENTARY

An important publication by Zile and colleagues that have been long interested in diastolic properties of the heart, confirms that diastolic heart failure (DHF) is a real entity and is associated with significant abnormalities of active relaxation and passive stiffness in the left ventricle (LV). Zile et al performed a sophisticated analysis of 47 individuals with clinical diastolic heart failure (normal LV systolic function and CHF), using diagnostic cardiac catheterization with high-fidelity micromanometer catheters, and measurements of a variety of LV diastolic pressure and volume phenomena. The patients met criteria for congestive heart failure and had no secondary cause of cardiomyopathy. Echocardiographic markers of diastolic function were not used for patient selection. There were 31 men and 16 women with a mean age of 59 ± 12 years. Ten control patients undergoing cardiac catheterization for chest pain evaluation were also studied; all had normal coronary arteries. The protocol involved research quality measurements assessing diastolic stiffness with a variety of techniques, including estimation of diastolic left ventricular pressure and volume throughout the entire period of diastole. The investigators' hypothesis was that patients with DHF would have an abnormally slow rate of ventricular relaxation, not allowing "full relaxation of the myocardium in early diastole." Thus, incomplete LV relaxation at the point of left ventricular minimal diastolic pressure would be a common denominator. Selected aspects of diastolic pressure-volume relationships, in addition to a number of calculated indices, including the corrected passive-stiffness constant, were measured. These included the time constants of isovolumic LV pressure decline (Tau); the minimal diastolic pressure pre A and post A wave; LV volume and mass; diastolic stiffness using pressure-volume coordinates; rate of relaxation, etc. The primary hypothesis was that the mean corrected stiffness constant in DHF patients would be 2 times as high as that of the control patients.

The results confirm Zile et al's belief that diastolic heart failure is a valid phenomenon substantiated by their highly sophisticated LV pressure-volume measurements. Of note, not all DHF patients had echocardiographic left ventricular hypertrophy. Relaxation parame-

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ters were abnormal, including Tau, LV early minimal diastolic pressure, and the relationship between the two. "Thus, relaxation was incomplete at the time of LV minimal diastolic pressure. . . by contrast, relaxation was complete at the time of LV minimal diastolic pressure in all controls." DHF patients had higher end-diastolic pressures and lower LV volumes than controls, consistent with increased chamber stiffness. The diastolic pressure-volume relationship was displaced upward and to the left. Zile et al conclude that the hypothesis that increased diastolic pressures and clinical heart failure in individuals with a normal ejection fraction are directly related to abnormal diastolic properties of the LV; and that the term "diastolic heart failure" is appropriate. They point out that pulmonary congestion and symptoms of dyspnea, as well as fatigue, are probably related to elevations in systemic venous tone and arterial pressure, particularly when blood shifts to the central circulation, increasing LV diastolic pressure. They stress that such individuals are particularly vulnerable to developing pulmonary edema. The abnormal passive stiffness of the ventricle allows for small changes in volume to induce large changes in LV diastolic pressure. Increased filling pressures in the LV result in decreased pulmonary compliance, increased work of breathing, and dyspnea. Zile et al suggest that abnormal exercise tolerance may be due to the high LV filling pressures during exercise; these individuals "have little or no increase in stroke volume during exercise." In this report, 38% of patients had echocardiographic LV hypertrophy, 70% had hypertension. These values are in keeping with other recent reports of diastolic failure, showing a prevalence of LV hypertrophy of < 50% and a high likelihood of associated hypertension. They stress that LV hypertrophy, while common in DHF, is not required for the diagnosis of DHF. The LV volume in these individuals is characteristically small. They conclude that the term "diastolic heart failure" is appropriate, and that the hemodynamic abnormalities confirmed in this study directly point to abnormal LV active relaxation and increased passive stiffness.

An accompanying editorial by Margaret Redfield stresses that DHF patients tend to be older and more likely to be female than in systolic heart failure; coronary artery disease is not a primary factor, and most patients have coexisting hypertension. Atrial fibrillation, fluid overload, or poorly controlled hypertension are precipitating factors for heart failure as well as for the exercise intolerance. The mortality in diastolic heart failure is "nearly equivalent" to that ofsystolic heart failure, a finding that has been seen in other data sets. She makes the point that neurohormonal and other abnormalities that are well characterized in systolic heart failure have not been adequately investigated in DHF. Some investigators have been unable to confirm impaired LV relaxation, and have questioned whether DHF is a real entity; Redfield, as well as the authors of the primary paper, believe that this issue has been laid to rest. She stresses that "without a better understanding of the pathophysiology of diastolic heart failure, opportunities for new and potentially more effective strategies may be missed" (Zile MR, et al. *N Engl J Med.* 2004:350:1953-1959).

## COMMENT BY JONATHAN ABRAMS, MD

This is an important investigation that confirms much previous data pointing to abnormal LV diastolic properties as being paramount in the causation of DHF. It is somewhat surprising to some, including myself, that diastolic heart failure carries a poor prognosis; the abnormalities described in this paper may help us to understand why prognosis is not benign. It is also important to note that echocardiographic LV hypertrophy is not a necessary component of DHF. Many individuals who have chronic kidney disease, particularly if they are on dialysis, will manifest diastolic heart failure. These patients may be particularly sensitive to volume changes with respect to clinical heart failure. In the absence of any overt clues leading to rare forms of heart failure, such as infiltrative disease, there appears to be no reason

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**VICE PRESIDENT/GROUP PUBLISHER:** Brenda Mooney.
**EDITORIAL GROUP HEAD:** Lee Landenberger.
**MANAGING EDITOR:** Robert Kimball.
**ASSOCIATE MANAGING EDITOR:** Christie Messina Petrone.
**MARKETING PRODUCT MANAGER:** Schandale Kornegay.

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**Editorial E-Mail:** christie.messina@ahcpub.com

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to perform myocardial biopsies or other studies; such individuals are probably more common than most physicians would realize. In summary, this is an elegant hemodynamic study in a substantial number of patients with apparently pure diastolic heart failure, which confirms that left ventricular relaxation and compliance properties are deranged in this condition. A common thread, other than the common association with hypertension, is not obvious. It is likely that the increased afterload of chronic hypertension alters LV myocardial function in individuals who manifest DHF. Therapy in these patients involves meticulous control of blood pressure and total body fluids; standard CHF drugs such as ACE inhibitors, beta-blockers, and even digoxin probably play a lesser role in treatment. Data on the most effective targeted treatments for DHF are lacking. ■

# Determinants of Survival in Atrial Fibrillation

ABSTRACT & COMMENTARY

***Synopsis:*** *Results of this study suggest that if an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might improve survival.*

**Source:** Corley SD, et al and the AFFIRM Investigators. *Circulation.*2004;109:1509-1513.

The AFFIRM study was a randomized comparison of 2 strategies for management of patients with atrial fibrillation. Patients with atrial fibrillation requiring therapy, who also had one or more risk factors for stroke or death, were randomized to either a rate control strategy of cardioversion and treatment with antiarrhythmic drugs or a rate control strategy using atrioventricular (AV) nodal blocking agents to control ventricular response. In this paper, Corley and colleagues report an "on-treatment" analysis of the relationship of survival to cardiac rhythm and treatment over time. In AFFIRM, 4060 patients were randomized over a 4-year period that ended on October 31, 1999. The mean duration of follow-up was 2.5 years with a maximum of 6 years. Patients in AFFIRM could be in sinus rhythm at the time of randomization. The initial results using an "intention to treat analysis" showed that there was no significant difference between rate control and rhythm control initial strategies. In this paper, an "on-treatment analysis" was used. For this purpose, a Cox proportional hazards regression was performed with evaluation of several time-dependent covariates. This allowed for drug therapies and heart rhythm at the time of follow-up visits to be evaluated and for multiple covariates to be included in a statistical model to assess each variable's relationship to the primary endpoint after adjustment or control for the other covariates. The analysis involved 6 time-dependent covariates: sinus rhythm, and the use of the following drugs, warfarin, digoxin, beta-blockers, calcium channel blockers, and rhythm control drugs. In addition to the 6 time-dependent covariates, 12 baseline variables were included in the analysis. These included: age at time of enrollment in the study, sex, gender, history of coronary artery disease, congestive heart failure, hypertension, diabetes, stroke or transient ischemic attack, smoking, first vs recurrent episode of atrial fibrillation, and the presence of either left atrial enlargement, left ventricular dysfunction, or mitral valve regurgitation on a 2-dimensional echocardiography. Since echocardiographic data were only available in a subset of 2796 patients, the analysis was carried out both with and without exclusion of the echocardiographic data. With echocardiographic data included, 12 covariates were identified that influenced survival. The following baseline variables were significantly associated with an increased risk of death: increasing age (HR = 1.06), history of coronary artery disease, (HR = 1.56), history of CHF (HR = 1.57), history of diabetes (HR = 1.56), history of stroke or TIA (HR = 1.70), recent history of smoking (H = 1.78), left ventricular dysfunction (HR = 1.36), and mitral regurgitation (HR = 1.36). Among the time dependent variables, the presence of sinus rhythm (HR = 0.53), warfarin use (HR = 0.50), digoxin use (HR = 1.42), and rhythm control drug use (HR = 1.49) were significantly related to survival after adjustment for other covariates. Results were similar if the echocardiographic data were excluded.

Corley et al believe that the their time-dependent analysis clearly shows that warfarin use improves survival, and that the presence of sinus rhythm, but not antiarrhythmic drug use, is associated with a lower risk of death. They then conclude that these results "suggest that if an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might improve survival."

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

The AFFIRM Study and several other trials on rate control vs rhythm control strategies have not shown any overall benefit with attempts to maintain sinus rhythm with antiarrhythmic drugs. This led the American College of Physicians to state in their new clinical guide-

lines that a rate control strategy was appropriate for most patients with atrial fibrillation (McNamara et al, *Ann Intern Med.* 2003;139:1018-1033). This report from Corley et al seems to counteract this position. However, the analyses in this study are quite complex. Although many baseline variables were included in the Cox regression model, any changes from baseline in a patient's condition, other than the time dependent variables that were analyzed, use of selected drugs and presence of sinus rhythm were not controlled. Corley et al seem to imply that maintaining sinus rhythm was an important determinant of survival. However, an alternative hypothesis, which they mention in their discussion but which might be overlooked, is that progressive disease is what determines whether antiarrhythmic drugs are likely to maintain sinus rhythm. Patients who deteriorate for whatever reason are likely to have recurrence of atrial fibrillation even if they continue antiarrhythmic therapy. Clinicians know that patients who switch back and forth are often less stable, and they also realize that the occurrence of significant disease, either cardiac or extra cardiac, often precipitates recurrences of atrial fibrillation. Thus, recurrent atrial fibrillation may just be a marker for patients whose overall status is declining. Atrial fibrillation may further complicate this decline but it may not be the primary driver.

For these reasons, I think the question of whether or not maintaining sinus rhythm will improve survival remains open. No one should argue that atrial fibrillation is a better rhythm than sinus rhythm. However, in the absence of complicating factors, it may not make much difference what rhythm a person is in as long as symptoms can be controlled and anticoagulation be maintained. ■

# Magnetic Remote Catheter Ablation

ABSTRACT & COMMENTARY

***Synopsis:*** *Remote magnetic navigation during radio-frequency ablation allows successful elimination of AV nodal re-entrant tachycardia in patients with dual AV nodal pathways.*

**Source:** Ernst S, et al. *Circulation.* 2004; 109: 1472-1475.

ERNST AND COLLEAGUES FROM ST. GEORGE HOSPITAL IN Hamburg, Germany describe a new technique for positioning and manipulating ablation catheters during electrophysiologic studies. The system is a remote magnetic navigation system, which uses 2 permanent magnets to move a specially designed catheter. The magnets are computer controlled and positioned on either side of the fluoroscopy table. By creating a relatively uniform magnetic field of 0.08 Tesla, an ablation catheter with a permanent magnet at the tip can be maneuvered within the patient's heart. By changing the orientation of the outer magnets, the magnetic field can be used to deflect the catheter tip. Since the fields are computer controlled, the magnetic field vectors can be stored and automatically re-applied to return the catheter to any prior position. A computer-controlled catheter advancement system was also used to move the catheter without the need for manual manipulation. To accomplish this, a video workstation is used with the operator manipulating the catheter using a joystick or mouse at a control station that may be outside the operating suite.

In this study, which was an early feasibility study, 42 patients underwent an ablation attempt for AV node reentrant tachycardia (AVNRT) with the use of the magnetic navigation system. Sheath insertions and placement of the diagnostic catheters were performed using standard techniques. This required a mean total of 12 ± 5 minutes with a radiation exposure of 3.4 ± 2.7 minutes. Subsequently the studies were performed with the physician-operator in a separate control room without need for lead protection. After confirming the mechanism of the arrhythmia, the right atrium close to the coronary sinus ostium was mapped for typical slow pathway potentials with the catheter manipulated solely by the magnetic navigation system. After mapping was completed, the site which gave the most favorable appearing slow pathway potential was determined and the field vectors with the best mapping result were then re-applied from the remote station to manipulate the catheter back to that site. Radio-frequency energy was then delivered and successful elimination of AV nodal reentrant tachycardia was produced in all patients. No recurrence was seen during a mean of 112 ± 48 days. No complications occurred.

Ernst et al conclude that remote magnetic navigation during radio-frequency ablation allows successful elimination of AV nodal reentrant tachycardia in patients with dual AV nodal pathways.

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

AVNRT is one of the easier arrhythmias to deal with in the electrophysiology laboratory. A successful slow pathway ablation can be achieved in more than 98% of cases and the risk of significant complication (usually

atrioventricular block) should be less than 1%. The magnetic remote catheter navigation system depicted here will not be a major addition for ablation procedures in patients with AVNRT, but has the potential to be very valuable for the ablation of more complex arrhythmias.

In ablation procedures where lines are required to break arrhythmia circuits, it is often tedious and difficult to create these lines with manual catheter manipulation. Long fluoroscopy exposures may be required and this forces the operator to stand wearing lead for long periods. With a truly effective remote navigation system, the fluoroscopy exposure can be markedly reduced and the operator can sit and manipulate the catheters from outside the room. Theoretically, it should also be easier to lay truly continuous ablation lines and eliminate all "leaks" that can lead to failure.

This early report on the use of the remote magnetic navigation system is highly promising. The real test of it will come when it is applied to more complex arrhythmias such as scar related atrial tachycardias, atrial fibrillation, and ventricular tachycardia. However, the early results are encouraging and we can look forward to rapid advances in the field. ■

# ACE Inhibitors in Aortic Stenosis

ABSTRACT & COMMENTARY

***Synopsis:*** *Enalapril improves effort tolerance and reduces dyspnea in patients with symptomatic aortic stenosis, but may cause hypotension in those with congestive heart failure, left ventricular dysfunction, or systolic blood pressure < 100 mm Hg.*

**Source:** Chockolingam A, et al. *Am Heart J.* 2004; 147:740.

Caution has been advised for vasodilator use in patients with significant aortic stenosis even in the presence of heart failure, yet there is little data on this issue. Thus, Chockolingam and colleagues enrolled patients with severe aortic stenosis (AS) and NYHA class III or IV dyspnea or angina. Severe AS was defined as valve area < .75 am², mean aortic gradient > 50 mm Hg, or Doppler peak velocity > 4.5 m/s. Exclusion criteria included hypotension (systolic blood pressure < 90 mm Hg or mean < 60) and renal dysfunction (creatinine > 2.5 mg/dL). After initial stabilization, patients were randomized to enalapril 2.5 mg twice daily titrated as tolerated to 10 mg twice daily or placebo in a 2:1 ratio. This was a double-blind study with a 4-week follow-up since most of the patients were awaiting surgery. The primary end points were development of hypotension, the Borg dyspnea index, and the 6-minute walk distance. Of the 61 patients who met eligibility criteria, 6 were eliminated for a variety of other issues. Among the remaining 56 patients, 37 were assigned to enalapril and 19 to placebo. Three patients in the enalapril group were withdrawn within 48 hours due to hypotension on 2.5 mg of enalapril; all 3 were in NYHA class IV heart failure, had moderate left ventricular dysfunction (EF < 40%), and had an initial systolic blood pressure between 90-100 mm Hg. One patient developed pulmonary edema after 2 weeks of enalapril, but was stabilized and continued on the drug. Four of the remaining 34 patients in the enalapril group had cough (11%), but continued the study. In the placebo group, 1 patient withdrew for worsening symptoms and 1 developed pulmonary edema. Despite the fact that many of the patients were taking potassium supplements or spironolactone, hyperkalemia was not observed. The Borg dyspnea index and the 6-minute walk distance improved in both groups, but the magnitude was greater in the enalapril group. Among the 43 patients (28 enalapril, 15 control) who continued on study medication for 12 weeks, the improvement on enalapril was sustained, but the placebo effect waned. Chockolingam et al concluded that enalapril improves effort tolerance and reduces dyspnea in patients with symptomatic aortic stenosis, but may cause hypotension in those with congestive heart failure, left ventricular dysfunction, or systolic blood pressure < 100 mm Hg.

### ■ COMMENT BY MICHAEL H. CRAWFORD, MD

There are 2 rationales for using angiotensin converting enzyme inhibitors (ACEI) in patients with AS. First, animal studies of aortic banding have shown reduced LV mass and preservation of systolic LV function. This preventative role may not apply to symptomatic patients near the end of their natural history in need of surgery. Second, patients with severe LV dysfunction and clinical decompensation due to severe AS have been shown to improve on IV nitroprusside. However, the patients in the study under discussion on average had normal LV function (mean EF, 63%) and were not decompensated. So this urgent therapeutic role may not apply. In fact, of the 8 patients in the enalapril group with heart failure symptoms, 5 improved and 3 were withdrawn because of hypotension. These 3 had moderate LV function impairment and systolic blood pressure < 100 mm Hg. Thus, it seems that only patients with angina symptoms (the majority in this study) seemed to benefit

from enalapril. It is difficult to understand the mechanism of this finding since more of the traditional measures of myocardial oxygen demand (heart rate, aortic valve gradient) did not change significantly and ACEI have not been shown to be antianginal. Also, this was an unusual AS population compared to the typical US patient in that only 5 patients had coronary artery disease and 9 had rheumatic heart disease. Another explanation is that the medical therapy (diuretics in many and dobutamine in some) made the real therapeutic difference, not the ACEI. The fact that the primary end points in the placebo group also improved supports this possibility. Chockolingam et al note that those with concomitant valvular regurgitation seemed to respond best, and 10 patients had grade 3 aortic regurgitation or more in the enalapril group vs 5 in the placebo group. Perhaps improved aortic regurgitation explains the greater benefit in the ACEI group. Chockolingam et al suggest that ACEI be considered for symptomatic patients with severe AS in whom surgery is delayed or not feasible, with the caution that it may cause hypotension in those with heart failure, low blood pressure, or reduced EF. Unfortunately, those with reduced EF or heart failure are the very patients we would like to get on ACEI. There are other approaches for those with angina. Thus, I don't see this study greatly changing our current approach to patients with symptomatic AS. ■

# Radial Artery Coronary Bypass Conduit

ABSTRACT & COMMENTARY

***Synopsis:*** *Using a radial raft, as opposed to a vein graft as the second bypass in patients receiving a LITA to the LAD, resulted in less late mortality without a lot of quality data to support it.*

**Source:** Zacharias A, et al. *Circulation.* 2004;109: 1489-1496.

THE SURVIVAL BENEFIT OF USING THE LEFT INTERNAL thoracic artery (LITA) to bypass the left anterior descending coronary artery (LAD), as compared to a saphenous vein graft, has been demonstrated. However, the best second choice is unclear, so Zacharias and colleagues from the Medical College of Ohio tested the hypothesis that a radial artery graft would be superior to a vein graft. This was retrospective observational analysis of their experience using propensity watching to overcome confounding effects. Between January 1996 and December 2002, there were 3161 isolated multigraft LITA-LAD bypass patients, of whom 1292 (41%) received a radial graft to the second vessel vs 1869 (59%) who received a vein. Since there were clinical differences between the 2 groups, 925 radial patients were propensity matched to vein patients. Perioperative outcomes were the same for both groups including death (1%). Cumulative 6-year survival was 92% for radial patients and 87% for vein patients (risk ratio, .68; $P < .03$). Repeat catheterization and revascularization rates were similar, but vein graft failure was higher than radial graft failure (41% vs 29%; $P = .04$). However, LITA patency was best with a failure rate of 6%. All LITA grafts were to the LAD. Chockolingam et al concluded that using a radial raft, as opposed to a vein graft as the second bypass in patients receiving a LITA to the LAD, resulted in less late mortality.

### ■ COMMENT BY MICHAEL H. CRAWFORD, MD

Based upon the improved survival of patients with LITA to LAD grafts, the concept of an all-arterial coronary bypass operation has emerged without a lot of quality data to support it. Although retropective, this is a well-done study that attempts to answer the limited question of whether the radial artery or a vein graft is the best second graft after a LITA to LAD. Using several statistical manipulations to match patients in a large database, the results show improved survival with the radial graft. These results parallel those of studies comparing using the right ITA vs a vein graft for the second vessel. However, now that the routine use of calcium blockers has eliminated the problem of radial artery spasm, there are several perceived advantages of the radial artery vs bilateral ITA grafts: 1) radials are larger; 2) easier to prepare; 3) can be harvested simultaneously with the LITA; 4) can reach remote arteries better than RITA pedicle grafts; and 5) decrease the incidence of sternal wound infection as compared to bilateral ITAs. Unfortunately, there has not been a direct comparison of the 2 all arterial approaches. Also, there is the issue of what to do for the third graft: 1) a piece of left over radial; 2) ITAs and a radial; 3) LITA, radial and an abdominal vessel (gastroepiploic, splenic); or 4) a vein. The use of a vein would increase the likelihood of a graft failure, so many prefer an all-arterial approach when feasible. This study lends more credence to this concept, but a prospective randomized trial would be more convincing. ■

# Diabetes and CABG

ABSTRACT & COMMENTARY

***Synopsis:*** *Tight glycemic control during surgery and 12 hours after CABG in diabetic patients improves perioperative outcomes and survival, and decreases wound infections and episodes of recurrent ischemia.*

**Source:** Lazar HL, et al. *Circulation.* 2004;109: 1497-1502.

Diabetics who undergo coronary artery bypass graft (CABG) surgery have increased perioperative and long-term morbidity and mortality. Although originally thought to be inevitable, there is now evidence that tighter glycemic control may improve outcomes in diabetics. Thus, Lazar and colleagues from Boston University sought to test the hypothesis that tighter glycemic control during CABG in diabetics would improve outcomes. They prospectively randomized 141 diabetic patients undergoing CABG to tight glycemic control (serum glucose 125-200 mg/dL) or standard therapy (glucose < 250). The tight control group received D5W with regular insulin and potassium IV just before surgery and up to the start of cardiopulmonary bypass. It was then restarted after the aorta was unclamped and continued for 12 hours. Then the patients resumed their preoperative diabetic regimens. The tight control group had a lower serum glucose (138 vs 260 mg/dL; $P < .001$); a lower incidence of atrial fibrillation (17% vs 42%; $P < .002$), and a shorter length of stay (6.5 vs 9.2 d; $P = .003$). Tight control patients had an increased survival over 2 years ($P = .04$), decreased episodes of recurrent ischemia (5 vs 19%; P = .01), and developed fewer wound infections (1% vs 10%; $P = .03$). Perioperative mortality was zero in both groups. Lazar et al concluded that tight glycemic control during surgery and 12 hours after CABG in diabetic patients improves perioperative outcomes and survival, and decreases wound infections and episodes of recurrent ischemia.

**COMMENT BY MICHAEL H. CRAWFORD, MD**

A glucose insulin and potassium (GIK) infusion has been shown in experimental myocardial infarct animal models to reduce ischemic injury. Although more difficult to control for confounders, human studies supported these findings. However, GIK never caught on in the treatment of acute myocardial infarction because of the overwhelmingly positive effect of reperfusion. Perhaps in the coronary surgical setting in diabetic patients it will find a role. This setting is almost like an animal model since blood flow to the heart is interrupted for a defined period of time and medications can be given before the major ischemic insult. Although even in this setting, it is unclear if GIK is necessary since other studies have shown benefit with insulin infusions alone. The important factor here may be glycemic control, which was achieved with GIK. Other studies in patients with acute ischemic syndromes have shown the deleterious effects of high blood glucose levels and the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed reduced mortality after acute MI in diabetics whose glucose was kept below 200 mg/dL. The exact mechanism of the benefit of lower blood sugar is unknown, but experimental studies suggest that high glucose levels may impair endothelial function, enhance inflammation, and augment thrombogenicity. It now seems clear that tight glucose control is important in acute ischemic syndromes and CABG. Several questions remain: Is the glucose and potassium necessary or is insulin enough? What is the ideal blood sugar level? Expect to see more studies in this important area. ■

# Procalcitonin in Infective Endocarditis

ABSTRACT & COMMENTARY

***Synopsis:*** *Procalcitonin may be a useful diagnostic marker in suspected IE.*

**Source:** Mueller C, et al. *Circulation.*2004;109: 1707-1710.

The diagnosis of infective endocarditis (IE) remains a challenge. Thus, these investigators from Basel, Switzerland hypothesized that a marker of systemic bacterial infection such as procalcitonin may help. In 67 consecutive patients with clinical suspicion of IE, a multidisciplinary team applied the Duke criteria to make the diagnosis of IE in 21 patients. Procalcitonin was significantly higher in the IE patients as compared to the others (6.6 vs 0.4 mg/mL, $P < .001$). The area under the receiver operating curve for procalcitonin was .86 vs .66 for C-reactive protein. The procalcitonin cutoff of 2.3 mg/mL showed a sensitivity of 81%, a specificity of 85%, a negative predictive value of 92%, and a positive predictive value of 72%. Multivariate analysis showed that procalcitonin was the only independent predictor of IE on admission to the hospital (OR, 1.52;

CI, 1.07-2.15, $P$ = .02). Mueller and colleagues concluded that procalcitonin may be a useful diagnostic marker in suspected IE.

■ **COMMENT BY MICHAEL H. CRAWFORD, MD**

The age of serum markers is upon us. Emergency department and other physicians in a triage capacity love these tests; they are quick, easy and usually have a high negative predictive value. So, if they are negative, the condition under suspicion can confidently be excluded. If the test is positive, it becomes someone else's problem and the low positive predictive value is of little concern to the triage physician. Procalcitonin seems to be another such test. As Mueller et al point out, it is just as good at diagnosing IE as BNP is for diagnosing heart failure. Heaven help us.

On the other hand, IE is as difficult to diagnose as ever and a negative procalcitonin may stave off a transesophageal endocardiogram (TEE) in an otherwise low risk patient. Many patients with signs of sepsis have normal cardiac histories, physical examinations and transthoracic echocardiograms because of IV drug use, compromised host defenses, and other illnesses put them at risk for IE despite relatively normal hearts. In such patients TEE may be the only way to make a diagnosis. The procalcitonin test may help direct further diagnostic efforts in these difficult cases. ■

# *CME Questions*

**34. The initial diagnosis of infective endocarditis is supported by:**
a. prolonged fever.
b. new heart murmur.
c. a high procalcitonin level.
d. all of the above

**35. A clear indications for ACEI in symptomatic patients with aortic stenosis is:**
a. congestive heart failure.
b. moderate-to-severe aortic regurgitation.
c. LVEF < 50.
d. all of the above

**36. Improved survival in atrial fibrillation patients is associated with:**
a. digoxin use.
b. warfarin use.
c. antiarrhythmic drug use.
d. all of the above

**37. Arrhythmia ablation catheters can be successfully manipulated now by:**
a. magnet.s
b. robots.
c. medical students.
d. all of the above

**38. Diastolic heart failure is characterized by:**
a. LV hypertrophy.
b. hypertension.
c. elevated LV diastolic pressure.
d. all of the above

**39. Survival after CABG in diabetics can be enhanced by:**
a. potassium infusion.
b. glucose infusion.
c. insulin to control blood sugar.
d. lasix to reduce lung congestion.

**40. After LITA to the LAD, the best second graft is:**
a. saphenous vein.
b. RITA.
c. radial.
d. splenic.

**Answers:** 34(d); 35(b); 36(b); 37(a); 38(c); 39(c); 40(c)

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**Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.***

# Missing Link Between Vaccines and Diabetes

A large cohort study from Denmark suggests no link between childhood vaccines and type 1 diabetes. The potential for such a link has been of concern for years because of the association between certain infections and the development of type 1 diabetes in children. Epidemiologists also noted that the incidence of type 1 diabetes has increased in developed countries along with a widespread use of vaccines in those countries. Danish researchers studied the records of children born in Denmark between 1990 and 2000, which represented 4,720,517 person-years of follow-up. In the cohort, 681 cases of type 1 diabetes occurred. The rate ratios for developing diabetes among children who received at least 1 vaccine compared to unvaccinated children were: 0.91 for *Haemophilus influenzae* type B vaccine, 1.02 for diphtheria/tetanus/polio vaccine, 0.96 for diphtheria/tetanus/pertussis/polio vaccine, 1.06 for whole cell pertus! sis, 1.14 for measles/mumps/rubella vaccine, and 1.08 for oral polio vaccine. No clusters of diabetes cases were found at any age level. The authors conclude that the data do not support the causal relationship between childhood vaccine and type 1 diabetes (*N Engl J Med*. 2004; 350:1398-1404).

## *Breast Cancer and the Use of Statins*

Adding to the considerable evidence regarding the safety and efficacy of statins, it now appears that statins may slightly reduce the risk of breast cancer. Published in the "Early View" online journal *Cancer*, this case-control study was designed to assess whether statins were associated with an increased risk of breast cancer. At least 1 previous study has suggested an increased risk of breast cancer with statin use. The study looked at 975 women in Washington state who were diagnosed with primary invasive breast carcinoma, and were between 65 and 79 years old at the time of diagnoses. The comparison group was 1007 randomly selected women from the same residence area. Compared with non-users, current users, or ever-users of statins were not found to be at an increased risk for breast carcinoma. And in fact, the odds ratio of statin users was 0.9 compared to non-statin users (95% CI, 0.7-1.2). Long-term statin use of > 5 years was related to an even lower odds ratio of 0.7. The authors conclude that statins are not associated with an increase risk of breast carcinoma, and may in fact impart a reduced risk among long-term users (*Cancer* April 26, 2004).

## *Warnings Issued for IBS Drugs*

Tegaserod (Zelnorm-Novartis), the heavily promoted serotonin 5-HT4 partial agonist for the treatment of irritable bowel syndrome (IBS), is the subject of new warnings by the FDA. The drug is indicated for women with IBS whose pri-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5413. E-mail: christie.petrone@thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

mary symptom is constipation. The warning is the result of reports of diarrhea leading to hypovolemia, hypotension, and syncope in a small number of patients. There have also been rare cases of bowel ischemia in patients taking tegaserod, although no causal relationship has been found. Novartis has issued a "Dear Doctor" letter regarding the change in labeling dated April 26 (for more information see www.FDA.gov/medwatch). This is the second IBS drug to come under FDA scrutiny. The serotonin 5-HT3 antagonist alosetron (Lotronex-GlaxoSmithKline), for the treatment of IBS in women with severe diarrhea, was briefly withdrawn from the market in June 2002 because of over 80 cases of ischemic colitis associated with use of the drug. Alosetron became available again in December 2002 under a restricted use program.

What is the risk of a re-prescribing penicillin to penicillin allergic patient? The risk may be quite low according to a new study. Researchers looked at a database from the UK General Practice Research Database which included over 3.3 million patients who received penicillin. More than 6000 patients reported an allergy to the initial prescription, however, 48.5% of those patients were given the second prescription for penicillin at least 60 days later. Of those 3014 patients, only 57 (1.89%) had another event after the second prescription. This was much higher than the rate of reactions in patients who had not had an initial reaction (odds ratio, 11.2; [95% CI 8.6-14.6]), however, the absolute rate of reactions in patients who had an initial allergic reaction was quite small (*J Allergy Clin Immunol.*2004:113; 764-770). An accompanying editorial pointed out that even anaphylactic reaction had a low rate of recurrence with repeat exposure (1 out of 16) (*J Allergy Clin Immunol.*2004:113;605-606). And, while no one is recommending rechallenging patients with penicillin allergies, the low rate of repeat reactions is a far cry from the reported 60% rate of previous studies

## FDA Actions

The FDA has removed the warning for lactic acidosis from metformin (Glucophage) and metformin extended release (Glucophage XR). Once considered the most serious side effect associated with metformin, a recent meta-analysis showed that there were no reports of lactic acidosis during more than 20,000 patient years use of the drug (*Arch Intern Med.*2003;163:2594-2602).

The FDA has approved apomorphine injection (Apokyn-Bertek) for hypomobility associated with Parkinson's disease. Hypomobility or "off periods" become more frequent with advanced Parkinson's disease and may occur at the end of a dosing interval or may occur spontaneously. A subcutaneous injection of apomorphine is effective for both types of “off periods.” However, because the drug causes severe nausea, it must be taken with an anti-emetic—although, not a 5HT3 antagonist because the combination may cause hypotension and syncope.

Aventis has received approval to market insulin glulisine (Apidra), a new rapid-acting insulin. The drug is a novel recombinant DNA human insulin analogue that is designed to be given 15 minutes before a meal or within 20 minutes after starting a meal. With a rapid onset and short duration of action, it is designed to cover mealtime blood sugar spikes. Aventis is marketing insulin glulisine to be used in combination with insulin glargine (Lantus), the company's long-acting basal insulin preparation.

The FDA has approved changes in prescribing information for finasteride (Proscar-Merck) that include concomitant use of the alpha-blocker doxazosin for the treatment of benign prostatic hyperplasia. Finasteride is a 5-alpha-reductase inhibitor. The combination was recently found to be better than either drug alone in reducing the overall clinical progression of benign prostatic hyperplasia (NEng J Med.2003;349:2387-2398).

Telithromycin (Ketek-Aventis) has been approved by the FDA for marketing for the treatment of community-acquired pneumonia including pneumonia caused by drug-resistant pneumococcus, sinusitis, and acute exacerbations of chronic bronchitis. Telithromycin represents the first of a new class of antibiotics known as ketolides. It is an oral tablet that is given once a day. ■