News and Views from the Literature

Peripheral Vascular Medicine

β-Blockers for Vascular Surgery and Angioplasty for Renal Artery Stenosis

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Two areas are explored in studies from the Netherlands: Myocardial infarctions (MIs) in high-risk patients undergoing vascular surgery, and the treatment of patients with both hypertension and renal artery stenosis.

The Effect of Bisoprolol on Perioperative Mortality and Myocardial Infarction in High-Risk Patients Undergoing Vascular Surgery

Poldermans D, Boersma E, Bax JJ, et al, for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group.
N Engl J Med. 1999;341:1789-1794.

The risk of fatal and nonfatal MIs in patients undergoing vascular surgery is higher than that associated with most other operations; many of these patients have coexisting coronary artery disease (CAD). Risk assessment relies on a careful history and physical examination (always), stress tests (often), and cardiac catheterization (occasionally) to identify patients at highest risk. A major issue, however, is how to reduce adverse cardiovascular outcomes.

The authors tested the hypothesis that a β-blocker, bisoprolol, would decrease the incidence of cardiovascular death and nonfatal MI in patients undergoing vascular surgery. After screening 1351 patients, they randomized 112 who had 1 or more cardiac risk factors (including age over 70 years, angina, prior MI, congestive heart failure, ventricular arrhythmias, diabetes, or decreased exercise tolerance, and also a positive dobutamine echocardiogram) to receive perioperative standard care or standard care plus bisoprolol. Notably, patients with extensive wall motion abnormalities on dobutamine echocardiography, indicative of left main or 3-vessel CAD, were excluded. Treatment with bisoprolol, 5 mg orally each day, was started at least 1 week preoperatively, increased up to 10 mg, and continued for 30 days postoperatively. The surgical procedures included aortic aneurysm repair, aortofemoral bypass, and infrainguinal arterial reconstruction. Of the 59 patients receiving bisoprolol, 2 (3.4%) died of cardiac causes, and none had a nonfatal MI. Of the 53 patients receiving standard care, 9 (17%) died of cardiac causes, and 9 (17%) had a nonfatal MI, resulting in a significant difference in a primary end point between the 2 groups ($P < .001$). The authors concluded that the perioperative use of bisoprolol reduces the incidence of death from cardiac causes and nonfatal MI in high-risk patients undergoing major vascular surgery.

This important study highlights the use of an aggressive medical management strategy. There are some major caveats, however. Foremost, patients with extensive wall motion abnormalities on dobutamine echocardiography were excluded. Whether these patients are best served by cardiac catheterization and subsequent coronary revascularization procedures before vascular surgery is not known. If left main CAD is suspected, clinical judgment determines whether to pursue further diagnostic studies and treatment. Therefore, the preoperative risk assessment in patients with cardiac risk factors should include a provocative test for myocardial ischemia. Also, although the 34% cardiovascular complications rate in the group receiving standard care seems inordinately high and exceeds that reported in many studies, this should not detract from the substantial benefit realized by the group who received bisoprolol. Taken together, a careful preoperative cardiac risk assessment and the intensive use of β-blockers will reduce the number of adverse cardiovascular events in patients undergoing vascular surgery.

The Effect of Balloon Angioplasty on Hypertension in Atherosclerotic Renal-Artery Stenosis

van Jaarsveld BC, Kalinen P, Pieterman H, et al, for the Dutch Renal Artery Stenosis Intervention Cooperative Study Group.
N Engl J Med. 2000;342:1007-1014.

Renal artery stenosis is a cause of hypertension as well as renal failure. The presence of renal artery stenosis in a patient

with hypertension, however, does not necessarily mean that management of the obstruction will lower blood pressure.

Van Jaarsveld and colleagues randomized 106 patients with both hypertension (despite treatment with 2 antihypertensive drugs) and renal artery stenosis (exceeding 50% secondary to atherosclerosis) to receive either percutaneous transluminal renal angioplasty (PTRA) (n = 56) or medical therapy (n = 50) and followed them for 12 months. The end points of the study were blood pressure, doses of antihypertensive drugs, renal function, and patency of the renal artery. Renal scintigraphy was abnormal in 65% of patients in each group, and renal artery stenosis exceeding 70% was present in 79% of the PTRA group and in 70% of the drug treatment group.

After 3 months, blood pressure was similar in the 2 groups, but patients receiving medical therapy were taking 3.2 ± 1.5 daily doses of antihypertensive drugs, compared with 2.1 ± 1.3 daily doses in the PTRA group ($P < .001$). Of the medical therapy group, 22 patients underwent PTRA at 3 months because of persistent hypertension. After 12 months, there were no differences between the groups in blood pressure, daily drug dose, or renal function. The renal artery was patent in all patients who received PTRA initially and occluded in 8 patients assigned to medical therapy. The authors concluded that PTRA has little advantage over antihypertensive drug therapy in the treatment of patients with hypertension and renal artery stenosis.

This study has several important flaws, and the authors' conclusion should be viewed cautiously. The coexistence of hypertension and renal artery stenosis does not mean that the 2 are causally related. In 35% of each group, renal scintigraphy was normal. In 21% of the angioplasty group and 30% of the drug therapy group, renal artery stenosis was less than 70%. This information suggests that there was not a pathophysiologic relationship between renal artery stenosis and hypertension in many of the patients. Also, 22 of 50 patients assigned to drug therapy crossed over to receive PTRA at 3 months. Stent placement was not part of the original protocol design. It is not known how many of these patients had ostial lesions, in which stents have been shown to improve long-term patency.

Given these problems, the authors have not adequately shown that PTRA in patients with hemodynamically significant renal artery stenosis and difficult-to-manage hypertension is not as effective as medical therapy for management of hypertension. What they have demonstrated, however, is that the routine use of PTRA in patients with both renal artery stenosis and hypertension may not be appropriate. These patients require careful medical evaluation before endovascular intervention is considered. For those in whom a pathophysiologic relationship between hypertension and renal artery stenosis is likely, it is reasonable to consider renal artery revascularization.

Electrophysiology

Congenital Long QT Syndrome

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The congenital long QT syndrome (LQTS) is an inherited disorder manifested clinically as recurrent syncopal episodes and a propensity for sudden arrhythmic death, frequently triggered by heightened adrenergic states.[1,2] The prolonged ventricular repolarization observed in this process has been linked to multiple genetic defects. In the LQT-1 genotype, the abnormality is caused by a defect on chromosome 11; LQT-2 has been traced to abnormalities of chromosome 7, and LQT-3 is related to abnormal genes on chromosome 3 regulating inactivation of sodium channels. Other genetic defects have been less completely characterized. For years, β-adrenergic blockade has been the mainstay of therapy for symptomatic patients with this disorder and for their relatives who are at high risk for a malignant arrhythmia.[3,4] Patients with this syndrome have also been treated over the years with permanent physiologic pacing,[5] surgical left cervicothoracic sympathetic ganglionectomy,[6,7] and implantable cardioverter-defibrillators.[8] Although retrospective data have been available, there has not been a clear examination of the effectiveness of β-blockers. Because a randomized trial examining the effect of these agents in LQTS would be impossible, Moss and colleagues reviewed the clinical effectiveness of β-blockers in LQTS patients enrolled in the International LQTS Registry. In doing the study, they hoped to identify risk factors for syncope, aborted cardiac arrest, and mortality during β-blocker therapy.

Effectiveness and Limitations of β-Blocker Therapy in Congenital Long-QT Syndrome

Moss AJ, Zareba W, Hall WJ, et al.
Circulation. 2000;101:616-623.

The study population comprised 581 probands with LQTS and 288 of their affected family members for whom β-blocker therapy was prescribed before age 41. The genotype was available in 139 LQTS patients (69 LQT-1, 42 LQT-2, and 28 LQT-3). To establish the effect of β-blocker therapy, a matched analysis was performed. The occur-

rence of unexplained syncope, aborted cardiac arrest requiring cardiac resuscitation, unexplained sudden death before the age of 41, and sudden death during LQTS-related surgery were examined during periods of equal duration before and after starting β-blockers. Chi-square, Wilcoxon signed rank, and Cox proportioned hazards methods were used, as appropriate, to compare events, make numeric comparisons, and establish specific risk factors, respectively.

Patients were treated with atenolol (65 ± 44 mg), metoprolol (121 ± 125 mg), nadolol (79 ± 64 mg), or propranolol (108 ± 86 mg) each day. Probands had a higher frequency of congenital deafness, overall symptoms, slower baseline heart rates, and longer QTc intervals before treatment than had affected family members.

The investigators found that β-blockers significantly reduced the number of cardiac events, the number of events per patient, and the event rate per patient per year ($P < .001$). This effect was most evident in the patients with the highest pre–β-blocker event rates. Nevertheless, 10 probands and 10 family members died after starting treatment with β-blockers. Death was not caused by discontinuation of medication during the treatment period.

While the use of β-blockers resulted in a significant decrease in event rates in LQT-1 and LQT-2 patients, there was no evident effect of β-blockers on events in the small number of patients with LQT-3. This is of interest, since these patients tend to have events at night, in the absence of clear-cut adrenergic provocation.

The decline in event rates was similar across a variety of doses of β-blockers. Using a Cox proportional hazards model, risk was higher in those patients in whom β-blocker therapy had been initiated at a young age. For those patients with syncope only or aborted cardiac arrest before starting β-blockers, the hazard ratios for any cardiac event for patients taking β-blockers were similar (6.0 and 5.1, respectively).

The dominant risk factor for experiencing an abortive cardiac arrest or death for patients receiving β-blockers was a pre–β-blocker history of aborted cardiac arrests. The hazard ratio was 12.9 in patients who had a prior aborted cardiac arrest but was still 3.1 in patients with a prior history of syncope only. The estimated cumulative probability of experiencing syncope, aborted cardiac arrest, or LQTS-related death on prescribed β-blockers is as noted in the Figure. Two thirds of the 33 deaths occurred in female patients, 79% of patients had 1 or more cardiac events before starting β-blockers, and 30% had 1 or more aborted cardiac arrests. Other variables that did not significantly contribute to risk included proband/affected family member status, QTc, congenital deafness, gender, heart rate, other therapy, and family history of LQTS-related death.

It was not surprising to see a significant reduction in the rate of cardiac events on β-blocker therapy in this study. This has been shown in previous studies involving the International LQTS Registry. Of concern was the estimation that patients who are symptomatic before initiating therapy with this agent have a very high likelihood of experiencing a recurrent cardiac event (32% within 5 years) despite treatment. Of even greater concern is the probability that 14% of patients with an abortive cardiac arrest before β-blocker therapy will experience an additional arrest or death within 5 years of beginning treatment with the drug.

On first inspection, it would be tempting to hasten to the conclusion that all symptomatic LQTS patients should receive a defibrillator. Before doing this, several limitations of this study should be noted:

- This was not a randomized trial during which the potential event rate in the absence of therapy could be established.
- Case-controlled analysis was not performed because of the limited number of high-risk patients in the Registry who were not treated.
- Chronologic bias could be present. Early patients may have been treated differently than later patients.
- Compliance of patients with their β-blocker therapy could not be established.
- Varying dosages of β-blockers were used, although there seemed to be little difference in the effect of a wide dosing range in patients receiving propranolol.
- Absence of any dose-response effect with drug therapy further suggests significant study limitations.

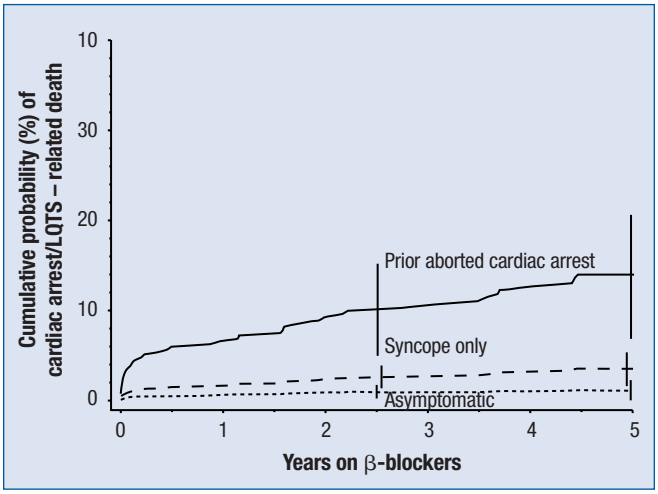

Figure. Estimated cumulative probability of experiencing aborted cardiac arrest or death on β-blocker therapy in patients with long QT syndrome (LQTS) who were asymptomatic (dotted line), had only syncope (dashed line), or had experienced aborted cardiac arrest (solid line) before β-blocker treatment. Risk curves are for LQTS patients started on β-blockers when aged 10 or older; the risk curves are higher for those started at a younger age. Time periods when patients are off therapy for more than 2 days are excluded.

- Recurrent syncope was counted in the overall recurrent event calculations. Many of these recurrent syncopal events could have non-LQTS etiologies.

The notion that β-blockers should have a beneficial effect in patients with LQTS is predicated on the belief that malignant ventricular arrhythmias are triggered by an adrenergic mechanism. While this idea is supported by phenotypic presentations seen in patients with LQT-1 and LQT-2 genotypes, multiple other mechanisms may also be operative. The absence of any drug effect in LQT-3 patients, who typically have events during sleep, is not surprising. Because the number of patients with this genotype was small, the authors stopped short of making any sweeping recommendations regarding β-blocker therapy in this group.

Certainly, the weight of data suggests that cardiac event rates may remain unacceptably high in β-blocker–treated patients who have had prior symptoms. Long-term pacing may be ineffective; 6 patients who died after the initiation of β-blockers had previously undergone pacemaker implantation. Based on analysis of the International LQTS Registry, this represents 25% of the 24 patients so treated. Fortunately, asymptomatic patients appear to do well in terms of cardiac arrest or LQTS-related death.

Since those patients with a previous aborted cardiac arrest are at substantial risk, implantation of a defibrillator is strongly recommended. It is more difficult to mandate defibrillator therapy in patients with a previous history of syncope. Only those patients with such a history remain at higher risk for any cardiac event, including syncope, and have a 3-fold increase in risk of cardiac arrest or LQTS-related death.

Based on the results of this paper, defibrillator implantation now appears to be a reasonable option in LQTS patients with previous syncope but is without the mandate present in patients with previous cardiac arrest. Such a recommendation is particularly meritorious in those patients with an apparent LQT-3 genotype, in whom β-blockers had the least effect. Previous studies have suggested that this group shows an increased QT interval with a prolonged, straight ST segment.[9]

Unfortunately, the ECG characteristics are not pathognomonic for specific genotypes and cannot be used to definitively categorize patients with this process. In addition, it remains difficult to obtain genetic characterization quickly in these patients, and at least 50% of LQTS patients do not fit neatly into these 3 genotypic categories. Until better means to characterize LQTS patients are available, their management will remain difficult. These data can be used as an increasing rationale for aggressive management of symptomatic patients.[4] Those patients with a previous cardiac arrest should be managed with an implantable defibrillator; those with previous syncope may also be appropriate device candidates.

References

1. Moss AJ, Schwartz PJ, Crampton RS, et al. The long-QT syndrome: prospective longitudinal study of 328 families. *Circulation*. 1991;84:1136-1144.
2. Moss AJ, Robinson J. Clinical features of idiopathic long QT syndrome. *Circulation*. 1992;85(suppl I):1140-1144.
3. Schwartz PJ, Locati E. Idiopathic long QT syndrome: pathogenetic mechanisms and therapy. *Eur Heart J*. 1985;6(suppl D):103-114.
4. Moss AJ. Management of patients with the hereditary long QT syndrome. *J Cardiovasc Electrophysiol*. 1998;9:668-674.
5. Moss AJ, Liu JE, Gottlieb S, et al. Efficacy of permanent pacing in the management of high-risk patients with long QT syndrome. *Circulation*. 1991; 84:1524-1529.
6. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *N Engl J Med*. 1971;285: 903-904.
7. Schwartz PJ, Locati E, Moss AJ, et al. Left cardiac sympathetic denervation in the therapy of the congenital long QT syndrome: a worldwide report. *Circulation*. 1991;84:503-511.
8. Groh WJ, Silka MJ, Oliver RP, et al. Use of implantable cardioverter-defibrillators in the congenital long QT syndrome. *Am J Cardiol*. 1996; 78:703-706.
9. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation*. 1995;92: 2929-2934.