



This Week in the Journal

October 24, 2002

OUTCOME	ODDS RATIO (95% Confidence Interval)
Death from any cause	0.45 (0.35-0.58)
Cardiac events	
Myocardial infarction	0.45 (0.35-0.58)
Congestive heart failure	0.45 (0.35-0.58)
Death from cardiac causes	0.45 (0.35-0.58)

0.0 0.5 1.0 1.5
Aspirin Better Aspirin Worse

Aspirin and Mortality from Coronary Bypass Surgery

In patients undergoing coronary-artery bypass surgery, aspirin is often avoided during the perioperative period because of concern about bleeding. This large, multicenter, observational study found that aspirin therapy initiated within 48 hours after surgery was associated with reduced mortality and fewer ischemic complications affecting the heart, brain, kidneys, and gastrointestinal tract. There was no excess bleeding.

These findings are provocative, but they were not derived from a randomized trial and are therefore subject to undetected bias. The substantial reduction in mortality with aspirin therapy is very important but must be confirmed in a randomized trial before aspirin therapy becomes routine.

see page 1309 (editorial, page 1359)

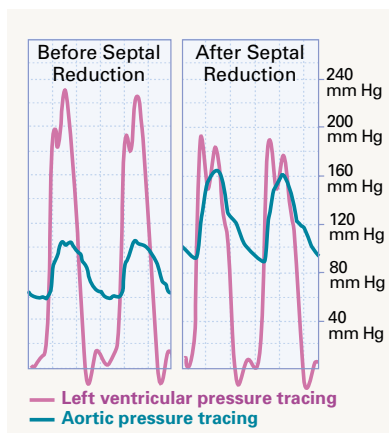
“Our data provide reassurance that neither total nor subtotal abdominal hysterectomy adversely affects pelvic organ function.”

Subtotal versus Total Abdominal Hysterectomy

A total of 279 women who were referred for hysterectomy because of benign disease were randomly assigned to undergo subtotal or total abdominal hysterectomy. Twelve months after surgery, the two groups had similar improvements in urinary symptoms and measures of urodynamic testing; neither type of surgery had adverse effects on bowel or sexual function. Total abdominal hysterectomy resulted in a longer hospital stay. Cyclical bleeding occurred postoperatively in 7 percent of the subtotal-hysterectomy group.

These data provide reassurance that neither total nor subtotal abdominal hysterectomy is likely to have an adverse effect on bladder, bowel, or sexual function, although longer follow-up is needed to clarify the risk of cervical prolapse after surgery.

see page 1318 (editorial, page 1360)



Nonsurgical Reduction of the Septum in Hypertrophic Cardiomyopathy

Some patients with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction do not have a response to medical therapy with beta-blockers or calcium-channel blockers. Surgical myomectomy is sometimes recommended. These investigators report preliminary observations on nonsurgical reduction of the hypertrophied septum by the injection of alcohol into the septal perforator vessels, causing controlled infarction of the septum.

This procedure was effective in reducing outflow tract obstruction and improving functional capacity. The observations are important, but the procedure must still be regarded as experimental and should be reserved for carefully selected patients.

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PERSPECTIVE

Hypertrophic Cardiomyopathy — The Benefits of a Multidisciplinary Approach

In the late 1950s, two sets of observations led to the recognition of a new cardiac disease. One was the discovery, by cardiovascular surgeons and cardiologists, of patients with subaortic pressure gradients at cardiac catheterization but without evidence of anatomical obstruction at surgery. These patients' hearts were also markedly hypertrophied. Simultaneously, pathologists and cardiologists described families in which several members had died suddenly and unexpectedly and were found to have hypertrophied hearts at autopsy. These seemingly unrelated observations rapidly came together and led to the delineation of what is now called hypertrophic cardiomyopathy. This condition has captured the attention and engaged the creativity of cardiovascular specialists working in a variety of disciplines, all of whom have made distinct contributions to the understanding of various aspects of this condition and its treatment.

The pathology consists of marked left ventricular hypertrophy, usually with a massively thickened septum, a small cavity, and a disarray of myocardial fibers and myofibrils. In one fourth of patients, the pathophysiology involves dynamic obstruction of outflow. Stimuli that reduce ventricular volume — such as those that enhance myocardial contractility — intensify or even provoke an intraventricular pressure gradient. Al-

most all patients have diastolic dysfunction with impaired ventricular filling.

Clinically, hypertrophic cardiomyopathy presents with a constellation of specific physical findings, including a rapidly rising arterial pulse and an early systolic murmur whose intensity and duration vary with the severity of obstruction. Echocardiography usually reveals an asymmetrically hypertrophied septum that causes obstruction when it is apposed by the anterior leaflet of the mitral valve during systole. Death is frequently sudden in patients with hypertrophic cardiomyopathy and is most commonly caused by ventricular fibrillation.

Hypertrophic cardiomyopathy is transmitted in autosomal dominant fashion. Researchers have found multiple mutations in 10 different sarcomeric proteins (such as myosin heavy chain and tropomyosin) that can cause the disorder. Some mutations confer an especially high risk of heart failure or arrhythmias. Hypertrophic cardiomyopathy is the most common monogenic cardiac disorder and the most common cause of sudden cardiac death in children and adolescents.

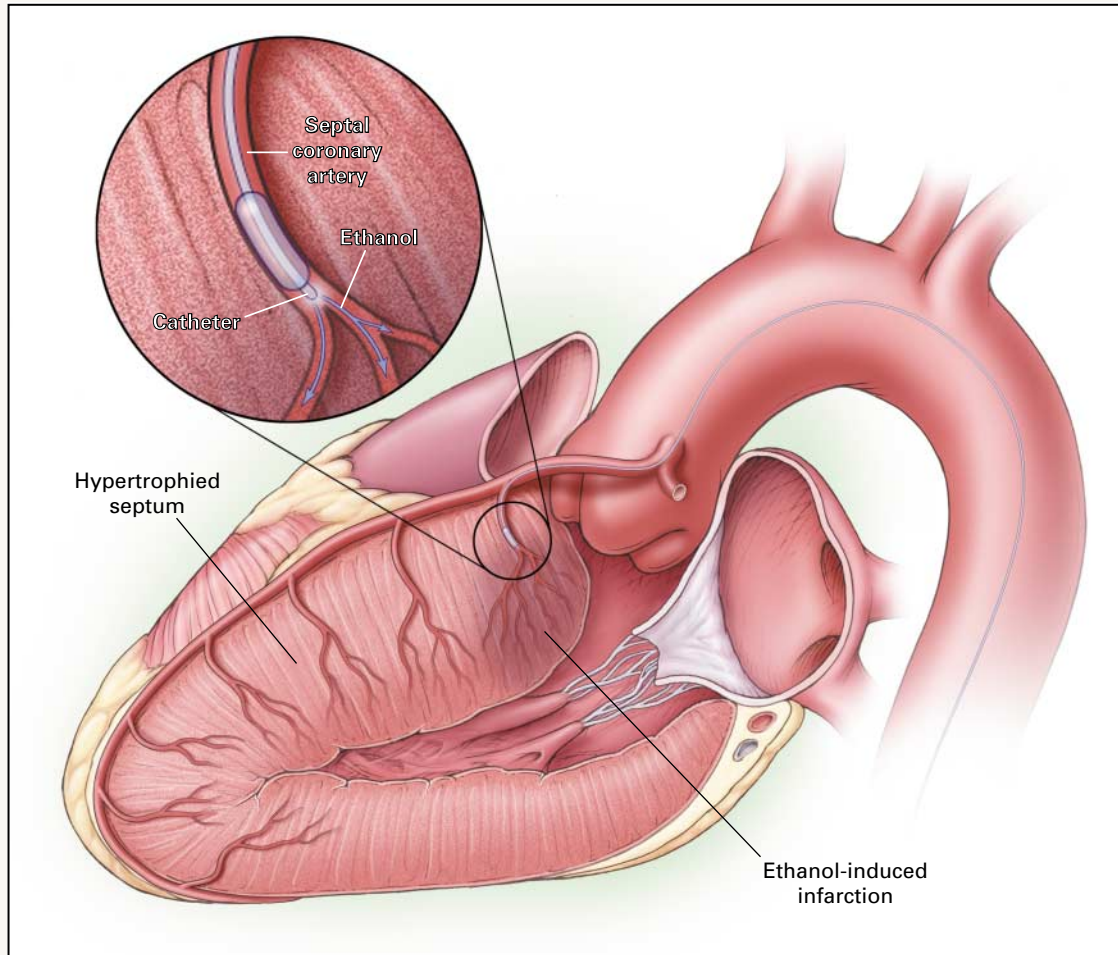
A variety of therapeutic options have evolved. An understanding of the importance of myocardial contractility in determining the severity of left ventricular outflow tract obstruction has led to the use of negative inotropic agents to reduce obstruction. Thus, beta-blockers, nondihydropyridine calcium-channel antagonists, and disopyramide are first-line therapies for patients with symptomatic outflow tract obstruction. Surgery involving incision into and resection of small portions of the hypertrophied septum relieves obstruction very effectively in the majority of patients in whom drug treatment fails.

Another option is dual-chamber

pacing. Preexcitation of the right ventricle alters the synchrony of ventricular contraction, thereby reducing obstruction. However, this approach is effective in only a minority of patients. Device therapy with an implantable cardioverter-defibrillator, on the other hand, is extremely effective in preventing sudden death from cardiac causes. Patients who have been resuscitated after cardiac arrest, who have sustained ventricular tachycardia during electrophysiological testing, or who have nonsustained ventricular tachycardia on Holter monitoring and patients with massive ventricular hypertrophy are at high risk for sudden death and are candidates for this treatment.

The most recent addition to the therapeutic armamentarium is non-surgical septal reduction, in which an infarction is produced in the upper interventricular septum by injection of ethanol through a catheter inserted into the septal coronary artery (see Figure). The resulting decrease in septal thickness reduces or even eliminates the intraventricular obstruction. The hemodynamic and clinical improvements that follow rival those achieved with surgery, but with fewer complications, a much shorter hospital stay, more rapid recovery, and less expense. In this issue of the *Journal*, Shamim and associates (pages 1326–1333) show, for the first time, that this procedure produces sustained reductions (lasting an average of three years) in the outflow tract pressure gradient and improvement in exercise capacity.

However, a number of caveats must be considered. First, there is a steep learning curve for physicians, who will need to acquire the considerable skill required to cannulate the septal artery. Second, although the associated mortality is low (up to 4 percent), it is similar to that



Section of Hypertrophied Left Ventricle.

The inset shows a balloon occluding the septal coronary artery and alcohol-induced septal infarction.

associated with surgery. Third, complete atrioventricular block requiring the insertion of a permanent pacemaker occurs in about one fourth of patients. Fourth, a dreaded, albeit uncommon, complication is massive myocardial infarction due to the escape of ethanol from the target vessel. Finally, nonsurgical reduction of the septum does not permit correction of accompanying mitral regurgitation. Despite these problems, reduction with ethanol

represents an important new therapeutic approach.

What of the future? Genetic diagnosis, classification according to mutation, and risk stratification are possible but not yet widely available. Studies of the natural history of hypertrophic cardiomyopathy in larger numbers of patients with specific mutations should be used to identify those at high risk for future events, asymptomatic carriers in whom pharma-

cologic intervention might retard or even prevent the development of hypertrophy, and nonaffected family members whose anxiety can be allayed. Management of diastolic dysfunction remains a major challenge and should also be the focus of intensive investigation.

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“Our findings suggest that a reevaluation of the process of contracting for clinical research is urgently needed.”

Special Article: A National Survey of Contract Provisions

In 2001, the International Committee of Medical Journal Editors (ICMJE) called for independence of authors from industry sponsors and full disclosure of the sponsors' role in research. This national survey reveals that the vast majority of medical schools' clinical-trial agreements with industry sponsors do not adhere to the ICMJE guidelines regarding trial design, access to data, and publication rights.

Many current contracts between industry and medical schools have not adequately safeguarded the integrity of privately funded biomedical research. Contracting officers at medical schools and hospitals need to be diligent in ensuring the academic freedom of their investigators.

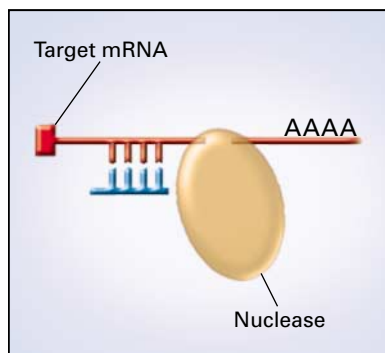
see page 1335 (editorial, page 1362)

“There are 800,000 new cases of diabetes per year, almost all of which are type 2.”

Clinical Practice: Type 2 Diabetes Mellitus

An asymptomatic 45-year-old Hispanic man has a fasting plasma glucose level of 142 mg per deciliter (7.9 mmol per liter) on initial evaluation and 139 mg per deciliter (7.7 mmol per liter) on reevaluation. Other than a steady gain in weight since college and borderline hypertension, his medical history is unremarkable. He is 175 cm (5 ft 9 in.) tall and weighs 95 kg (209 lb; body-mass index, 31.2), and his blood pressure is 138/88 mm Hg. Physical examination is notable only for abdominal obesity and absent ankle reflexes. How should this patient be treated?

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Clinical Implications of Basic Research: RNA Interference and HIV

A recently discovered type of RNA, small interfering RNA, silences messenger RNA (the transcript of an active gene) by binding to specific sequences in the messenger RNA. Small interfering RNAs can block the replication of HIV in vitro by triggering the degradation of specific viral messenger RNAs. This work reveals new possibilities for controlling not only HIV infection but also the growth of cancer cells.

The recent explosion of research on small interfering RNA signals the opening of an entirely new approach to the control of viral replication and tumor-cell proliferation.

see page 1364

“The welfare of the patient must prevail over all competing interests.”

Sounding Board: Collaborating with Industry — Choices for the Academic Medical Center

Ties between academic medical centers and commercial entities are increasing in number and magnitude. These ties have the potential to benefit the public through the development of novel diagnostic and therapeutic techniques. They can also be quite problematic, since the goals of an academic medical center and those of a commercial entity may differ in many respects. In this article, leaders of major academic medical institutions provide guidance on the successful management of several specific points of interaction.

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