AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

CLINICAL CARDIOLOGY ALERT®

A monthly update of developments in cardiovascular disease

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

EDITOR
Michael H. Crawford, MD
Robert S. Flinn Professor
Chief of Cardiology
University of New Mexico,
Albuquerque

EDITORIAL ADVISORY BOARD
Jonathan Abrams, MD
Professor of Medicine
Division of Cardiology
University of New Mexico,
Albuquerque

John DiMarco, MD, PhD
Professor of Medicine
Division of Cardiology
University of Virginia,
Charlottesville

Bernard J. Gersh, MD
Chief of Cardiology
Georgetown University
Medical Center
Washington, DC

Attilio Maseri, MD, FRCP
Institute of Cardiology
Catholic University
Rome, Italy

Gerald M. Pohost, MD
Professor of Medicine
Director
Division of Cardiovascular
Disease
University of Alabama
Medical School
Birmingham

Craig Pratt, MD
Associate Professor of
Medicine
Section of Cardiology
Baylor University
Chairman, Cardio-renal
Advisory Board
FDA

SPECIAL CLINICAL PROJECTS
Gideon Bosker, MD
Assistant Clinical Professor
Section of Emergency
Services
Yale University School
of Medicine

EXECUTIVE EDITOR
Glen Harris

ASSISTANT MANAGING EDITOR
Robin Mason

COPY EDITOR
Michelle Moran

Punching Holes in the Heart: Not Quite a Knockout

ABSTRACT & COMMENTARY

Synopsis: *The adoption of the transmyocardial laser revascularization procedure cannot be advocated. Further research will help to find out whether any subgroup of patients will benefit.*

Source: Schofield PM, et al. *Lancet* 1999;353:519-524.

A british trial of transmyocardial laser revascularization (TMLR) has recently been reported, which is the first randomized study of this technology compared to conventional medical therapy. A total of 188 patients with severe chronic stable angina who were poor or noncandidates for coronary bypass surgery or angioplasty were randomized to optimal anginal therapy or TMLR plus anti-anginal therapy; patients were enrolled between 1993 and 1997. Follow-up was for at least one year; no crossovers occurred. The primary outcome was exercise test duration at 12 months. A variety of secondary outcomes were assessed, including physician and patient angina class assessment; a 12-minute walk test; hospitalization for unstable angina; cardiovascular death; ejection fraction; and exercise methoxyisobutyl isonitrile (MIBI) radionuclear scans. All end points were assessed at 12 months. A priori improvement on stress testing was defined as a 50% increase in maximum exercise time. All patients had chronic angina (all with inducible ischemia), relatively normal LV function, and were unsuitable for conventional revascularization. TMLR was carried out with a carbon dioxide laser (PLC Medical Systems) through a small anterolateral thoracotomy adjacent to the area of reversible ischemia as identified on nuclear stress testing. Approximately 30 channels were made per patient (range, 6-75), each approximately 1 mm in diameter, with a distribution of approximately 1 per cm^2. An independent data monitoring committee met on two occasions and chose to continue the trial until 190 patients were recruited. The patient population was predominantly male, approximately 60 years of age, with Canadian Class III angina (73%) or Class IV (27%) angina. Ejection fraction was approximately 50%. Three-fourths had had a prior myocardial infarction and almost all had had prior coronary bypass grafting. Twenty-five percent had had a

INSIDE

Prognostic value of dobutamine stress echo
page 27

Electrophysiologic effects of adenosine in patients with SVT
page 28

Pulmonary venous flow reversal in MR
page 29

PTCA. Almost 20% were diabetic. Medical therapy consisted of conventional anti-anginal medications. Calcium antagonists were used in more than 90% at baseline, declining to 85% at 12 months in the TMLR subjects, and 100% of medically treated patients at one year. Nitrate use declined in the TMLR patients as opposed to the medical group.

The main results are not impressive. Survival was not different—89% in the TMLR cohort and 96% in the medical cohort at 12 months. Perioperative mortality for TMLR patients was 5%. Mean hospital stay was 10-11 days; there was significant morbidity in the TMLR group, with one-third having some type of infection. Exercise time was approximately 40 seconds shorter in the TMLR group, at each testing interval (3, 6, 12 months, none statistically significant). Patients stopped more frequently for angina in the medical cohort, and more for dyspnea or fatigue in the TMLR patients. TMLR patients did not walk greater distances on the 12-minute walk test at 12 months, but these patients did walk farther at three and six months. More TMLR subjects achieved a reduction in Canadian angina class as assessed by physicians; however, on an angina scale recorded by patients, there was less difference in chest pain frequency. TMLR patients had fewer unstable angina admissions at 12 months. Both groups demonstrated a decrease in segments with reversible ischemia and an increase in irreversible ischemic myocardial segments. Ejection fraction was essentially unchanged. Schofield and colleagues conclude that "there were no clinically important differences between groups in treadmill exercise time or 12-minute walking distance." There was a modest improvement in angina in TMLR patients. TMLR carried a significant burden of morbidity and mortality, particularly in the early postoperative period. Schofield et al strike a cautionary note about the procedure as well as the costs of new technologies in countries with limited resources. They also stressed the lack of industry funding for trials with devices and the possible selection of patients away from clinical trials to institutions who offer as yet unproven technology. They conclude, "The adoption of the TMLR procedure cannot be advocated. Further research will help to find out whether any subgroup of patients will benefit."

COMMENT BY JONATHAN ABRAMS, MD

This is a sobering report of significance to those who were hoping that laser revascularization would represent a boon for patients with angina pectoris who are not candidates for further revascularization procedures. Nevertheless, the case is not necessarily closed, in that there are now a number of trials under way assessing catheter-based laser revascularization. The first reports of TMLR in a cardiac surgery setting appeared in 1995. Several nonrandomized studies have been reported, most of which were quite promising, but none were truly randomized to include a cohort of medically treated subjects. In addition to the high-energy carbon dioxide laser, Homian Yag laser systems are currently under investigation. The Food and Drug Administration (FDA) has approved the CO2 PCL laser and the Eclipse Homian Yag unit for surgical use only. Data from two large studies with catheter-based systems (Eclipse, CardioGenesis) will be submitted to the FDA in the future. If this new concept of treatment of coronary artery disease using state-of-the-art technology is to be successful, it makes sense to use a percutaneous catheter-based system. Considerable experience is being accrued in the United States in randomized trials. While there is some morbidity, mortality does not appear to be a problem. Patients can be discharged from the hospital within 48 hours. At the recent American College of Cardiology meeting (March 8, 1999), the PACIFIC Trial was reported at a late-breaking trial session (S. Oesterle, MD), demonstrating favorable results with a non-FDA-approved Homian Yag catheter system (CardioGenesis). Two hundred twenty three patients were randomized to the laser or medical therapy. At six months, there was a significant improvement in angina status and exercise

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

GROUP PUBLISHER: Donald R. Johnston.

EXECUTIVE EDITOR: Glen Harris.

ASSISTANT MANAGING EDITOR: Robin Mason.

COPY EDITORS: Michelle Moran, Neill Larmore, Holland Johnson.

GST Registration Number: R128870672.

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

Copyright © 1999 by American Health Consultants. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

Back issues: $17. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue 's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: michelle.moran@medec.com

Subscription Prices

United States
$199 per year (Student/Resident rate: $100).
Multiple Copies
1-9 additional copies: $100 each. 10 or more copies: $60 each.
Canada
$243 per year plus GST (Student/Resident rate: $110 plus GST).
Elsewhere
$229 per year (Student/Resident rate: $110).

Accreditation

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials. **For CME credit, add $50.**

Questions & Comments

Please call **Robin Mason,** Assistant Managing Editor, at (404) 262-5517, or **Michelle Moran**, Copy Editor, at (404) 262-5589 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, a statement of financial disclosure of editorial board members is published with the annual index.

duration in the TMLR group compared to medical treatment. Other unpublished data are promising with catheter-based Homian Yag lasers. The use of fiber optic delivery catheters using fluoroscopic guidance by experienced interventionalists may have promise, particularly as the morbidity and mortality associated with surgical-based TMLR is not a factor.

We do not know how or why laser revascularization might be effective. The original premise that intramyocardial channels would remain open appears not to be valid. Angiogenesis and/or collateral development is a possibility, as is cardiac denervation. All cardiologists have patients in their practice who have undergone one or more revascularizations, often many, who have severe refractory stable angina, relatively preserved left ventricular function, and who are deemed to be nonrevascularizable. These individuals lead lives of quiet desperation. While TMLR does not appear to be a panacea to these patients, it may be that selected use of this procedure, particularly if catheter-based techniques turn out to be safe and effective, may provide important palliative improvement for such individuals, in whom a modest enhancement in exercise time and a decrease in angina frequency, even without complete elimination of ischemic symptoms, would be a real advance. If this can be done with a reasonable safety and cost profile, this truly would be an advance for this unfortunate group of patients. At the present time, the British trial dampens the enthusiasm for this approach, at least with laser energy delivered through a thoracotomy, while the just released PACIFIC Trial (catheter-based TMLR) is encouraging. ❖

Transmyocardial laser revascularization results in:

a. increased survival.
b. increased exercise performance.
c. reduced angina.
d. increased ejection fraction.

Prognostic Value of Dobutamine Stress Echo

ABSTRACT & COMMENTARY

Synopsis: *Dobutamine stress echocardiography provides added value over clinical parameters for predicting late clinical events during long-term follow-up and helps separate high- and low-risk patients with suspected or overt coronary artery disease.*

Source: Poldermans D, et al. *Circulation* 1999; 99:757-762.

The long-term prognostic value of dobutamine stress echocardiography (DSE) is poorly defined. Thus, Poldermans and associates evaluated 1734 consecutive patients referred for DSE and followed them for 6-96 (mean, 36) months. Excluded were 74 patients who had revascularization within three months and one patient lost to follow-up. Subsequent clinical events were assessed by physicians unaware of the DSE results. DSE with atropine, if necessary, was done in the standard fashion without stopping the patient's cardiac drugs. In 366 patients, 428 cardiac events occurred and included cardiac death in 108, nonfatal infarction in 128, and late revascularization in 192. There were no deaths or infarctions associated with DSE and only 4% of the patients developed severe hypotension. DSE was inconclusive (suboptimal heart rate and no ischemia) in 6%. The annual cardiac death or infarction event rate was 1.2% over five years in patients with a normal DSE and 5.4% in those with new (N) wall motion abnormalities (WMA) and 6.8% in those with both new and resting (R) WMA. Multivariate analysis showed that NWMA was the strongest predictor of all cardiac events (risk ratio [RR], 3.5). Cardiac death alone was best predicted by extensive RWMA (RR, 3.9) and only age added anything to the prediction (RR, 1.04). Revascularization alone was best predicted by hypercholesterolemia (RR, 4.0), then NRWA (RR, 3.3) and presence of angina (RR, 2.4). Poldermans et al conclude that DSE provides added value over clinical parameters for predicting late clinical events during long-term follow-up and helps separate high- and low-risk patients with suspected or overt coronary artery disease.

COMMENT BY MICHAEL H. CRAWFORD, MD

The prognostic value of DSE and stress echocardiography in general has been a perceived weakness of this technology that has been used by the proponents of stress nuclear perfusion imaging (NPI) to denigrate stress echo. Stress NPI is generally believed to be more sensitive, but less specific, than stress echo for the diagnosis of ischemia. The proponents of stress NPI have pointed out that a negative test is associated with a low incidence of future cardiac events (2.2%), whereas several studies have shown that a negative DSE is associated with a higher event rate (6.6-8.5%/yr). The definition of a negative stress NPI in these studies was a normal resting and stress NPI. When the same analysis was done in this study, the event rate for DSE was 1.3%/yr. Thus, the prognostic value of the two stress imaging techniques is similar and this should not be a basis for test selection.

Another perceived advantage of NPI is its ability to localize the coronary artery territory involved with

ischemia better than stress echo. Interestingly, in this study, ischemia location by DSE was not predictive of long-term outcome. On the other hand, the extent of ischemia was weakly predictive of outcome—one segment, RR = 2.9; two segments, RR = 4.0. This makes sense since the extent of ischemia would roughly correlate with postinfarction left ventricular dysfunction if infarction occurred in the ischemic area. Also, extensive RWMA correlated with left ventricular ejection fraction, which is related to survival. Thus, for long-term cardiac event prediction, the severity of ischemia and the extent of prior infarction may be more valuable than the location of ischemia. Consequently, the presumed ischemia localization superiority of NPI may not be critical for prognosis.

The 6% incidence of inconclusive studies is of concern with regard to the use of DSE, but it was mainly due to inadequate heart rate achievement in patients on beta blockers. Many physicians withhold beta blockers if feasible. Also, NPI studies have considered this a deficiency. In fact, NPI is touted to be highly accurate even in the event of suboptimal heart rate during stress. Whether this is a real advantage of NPI is difficult to tell. The new arbutamine delivery system may minimize inadequate heart rate responses and reduce inconclusive studies with DSE. Finally, harmonic imaging and contrast echocardiography may further enhance image quality and allow for more accurate stress echo studies. ❖

A negative resting and dobutamine stress echo is associated with an annual death or infarction rate of:

a. 1.2%.
b. 5.4%.
c. 6.8%.
d. 8.9%.

Electrophysiologic Effects of Adenosine in Patients with SVT

ABSTRACT & COMMENTARY

Synopsis: *The response to adenosine for tachycardia termination is of only limited value for defining either the mechanism of supraventricular tachycardia or the anatomic location of the arrhythmia in patients with atrial tachycardia.*

Source: Glatter KA, et al. *Circulation* 1999;99: 1034-1040.

In this paper, glatter and colleagues from the electrophysiology section at the University of California-San Francisco report the results of a retrospective analysis of the use of adenosine during electrophysiologic studies for supraventricular tachycardia (SVT) at their institution. Patients with atrial fibrillation, atrial flutter, and automatic junctional tachycardia were not included in the study. Two hundred twenty-nine patients with other forms of supraventricular arrhythmia received adenosine during the period reviewed. The principal diagnoses were as follows: typical AV nodal reentrant tachycardia (AVNRT)—82 patients; atrioventricular reentry (AVRT)—59 patients; atypical AVNRT—13 patients; permanent form of junctional reciprocating tachycardia—12 patients; atrial tachycardia—53 patients; and inappropriate sinus tachycardia—10 patients. Patients received the usual clinical doses of adenosine (6 mg or 12 mg) as a rapid bolus injection via peripheral vein during running tachycardia. Glatter et al then cataloged responses as either tachycardia termination, tachycardia suppression, AV block without effect on tachycardia, or no effect.

All patients with both AVRT and AVNRT had their tachycardias terminated after adenosine. The pattern of termination was somewhat variable. The most common pattern was block during anterograde conduction in the AV node. Block during retrograde conduction and termination of the tachycardia with premature complexes, however, were also seen. The latter was not usually a reproducible finding. Adenosine administration led to initiation of atrial fibrillation in nine of 59 patients with AVRT but in no patient with AVNRT.

In the atypical form of AVNRT, tachycardia termination usually occurred during retrograde conduction over the slow AV nodal pathway, but two tachycardias terminated in the fast pathway. In patients with permanent junctional reciprocating tachycardia (PJRT), three of 11 showed tachycardia termination in the AV node and eight in the retrograde pathway. No patient with atypical AVNRT developed atrial fibrillation, while two of 12 patients with PJRT developed atrial fibrillation. Responses to adenosine during atrial tachycardias were more variable. Fourteen of 24 automatic tachycardias were transiently suppressed by adenosine. Six of 20 tachycardias thought to be either triggered or reentrant were suppressed or terminated by adenosine. Site of origin did not determine response. All 10 patients with inappropriate sinus tachycardia showed an increase in sinus cycle length and three of these also had high-grade AV block. Among the patients with atrial tachycardia whose tachycardias were neither suppressed nor terminated, AV block was the observed response.

Glatter et al conclude that there are multiple possible effects of adenosine in patients with SVT. Therefore, they believe that the response to adenosine for tachycardia termination is of only limited value for defining

either the mechanism of the SVT or the anatomic location of the arrhythmia in patients with atrial tachycardia.

COMMENT BY JOHN P. DiMARCO, MD, PhD

When adenosine was first introduced, it was hoped that it might be a highly specific pharmacologic tool for evaluating the mechanisms of various arrhythmias. In supraventricular tissues, adenosine's primary effect is to increase the outward potassium current, which leads to hyperpolarization of the atrial cell, shortening of the atrial refractory period, and block of AV nodal conduction. In addition, adenosine has indirect anti-adrenergic effects to lower the intracellular levels of cyclic AMP produced in response to beta adrenergic stimulation.

During its development, it was hoped that since adenosine had such a short period of effect after intravenous injection, it could provide a specific probe for differentiating the mechanisms of arrhythmias. As shown by Glatter et al, there are significant limitations to the diagnostic uses of adenosine due to heterogeneity in both the substrate for arrhythmias and multiple effects of the agent itself.

Adenosine will continue to have some diagnostic role. Its diagnostic value will be most valuable in those situations where it produces a definite change. Increase in pre-excitation due to AV nodal block and production of AV block during ongoing tachycardia will continue to be useful diagnostic findings. Occasionally, it can be useful in patients with wide complex tachycardia in whom a supraventricular mechanism is strongly suspected. In most other situations, responses to adenosine will only provide mechanistic information of limited value.

It is also important to remember that use of adenosine is not without hazards. Glatter et al report a significant incidence of atrial fibrillation after adenosine injection. It appears that the incidence of atrial fibrillation is higher when it is administered during electrophysiologic studies than during clinical use, but other clinical reports of atrial fibrillation during treatment of SVT have appeared. Other potential pro-arrhythmic effects of adenosine include AV block and production of bradycardia-dependent polymorphic ventricular tachycardia under appropriate circumstances. Therefore, anyone planning to use adenosine infusions for diagnostic purposes should be prepared for these consequences and should recognize that the response observed will rarely be definitive. ❖

Injection of adenosine for supraventricular tachycardia:

a. reverts 50% of re-entrant tachycardias to sinus rhythm.
b. is rarely pro-arrhythmic.
c. is of limited diagnostic value for arrhythmia mechanism.
d. does not affect automatic tachycardias.

Pulmonary Venous Flow Reversal in MR

ABSTRACT & COMMENTARY

Synopsis: *Pulmonary venous flow reversal is a useful sign of severe mitral regurgitation, but its sensitivity is low.*

Source: Enriquez-Sarano M, et al. *Am J Cardiol* 1999;83:535-541.

The accurate, noninvasive determination of mitral regurgitation (MR) severity is challenging, yet of critical importance clinically. Systolic flow reversal in the pulmonary veins is part of the angiographic diagnosis of 4+MR (severe) and can be detected by pulsed Doppler trans-thoracic echocardiography. Thus, Enriquez-Sarano and colleagues evaluated the physiologic determinants of pulmonary venous flow (PVF) and the diagnostic accuracy of PVF reversal for severe MR in 128 patients with at least mild MR. The quantitation of MR was done by two methods: a quantitative Doppler determination of mitral and aortic stroke volumes and quantitative, two-dimensional echocardiography of the left ventricular and aortic stroke volumes. From these measurements, regurgitant volumes, fraction, and flow orifice were calculated. In the 128 patients, regurgitant fraction varied from 4% to 81% and PVF reversal in systole was observed in 39 patients. In a multivariate analysis, decreased PVF independently correlated with a larger regurgitant orifice, eccentric MR jets, longer jets, larger left atria, and lower MR velocity. In the patients with organic MR (not due to left ventricular dysfunction), increased filling pressures were associated with PVF reversal. For severe MR, defined as regurgitant orifice greater than 35 mm^2 and regurgitant fraction more than 50%, PVF reversal showed a sensitivity of 60% and a specificity of about 90%. Enriquez-Sarano et al conclude that in patients with MR, PVF reversal is complex and determined by MR severity, left ventricular filling pressure, jet characteristics, and left atrial volume. Thus, PVF reversal is a useful sign of severe MR, but its sensitivity is low.

COMMENT BY MICHAEL H. CRAWFORD, MD

Most echocardiography laboratories now routinely measure pulmonary venous flow (PVF). One major reason for this is to help with the determination of MR severity. Thus, this report on the value of PVF for determining MR severity is of interest. Systolic PVF was lower in MR patients vs. normals (4 vs 59 cm/sec) and the ratio of systolic to diastolic flow was lower (0.25 vs 1.6). However, there was considerable variability and the predictive value of PVF for determining MR severity is

low. PVF reversal was useful if present, but sensitivity was low for severe MR. The explanation for these disappointing results was that PVF has multiple determinants in patients with MR, including jet characteristics and left atrial volume. It seems obvious that whether an MR jet impinges on a pulmonary vein orifice would affect PVF, but the exact relationship is unclear even in this study. Also, it is well known that increased left atrial size can blunt the hemodynamic effects of MR upstream, keeping left atrial and pulmonary pressures low despite severe MR. Thus, it is not surprising that some patients with severe MR will have normal PVF.

This study exhibits different results than other studies that have shown a high correlation between PVF and MR severity, especially with PVF reversal. Some of the latter studies suffered from being small, select studies and others used an angiographic gold standard for severe MR, which included visualization of reversed flow of the angiographic dye in the pulmonary veins during systole. Not surprisingly, such studies showed a better correlation with Doppler PVF findings. This study used two Doppler echo gold standards that estimated regurgitant volume or the regurgitant fraction of total stroke volume. These techniques are imprecise and subject to error, but they do not suffer the tautologic problem of using an angiographic standard. Also, by using two measurement techniques, the precision of this study was enhanced. In addition, both techniques gave similar results, so the veracity of the conclusions is strengthened. Unfortunately, most echocardiographic laboratories do not attempt quantitation of MR severity because of the time required and the perceived imperfections in the techniques, relying instead on multiple criteria for MR severity, including color jet characteristics, chamber sizes, various velocities, estimated pulmonary pressure, and mitral apparatus deformities. This study and others suggest that quantitation of regurgitation should be used more frequently in those with at least moderate MR or more. ❖

Echo Doppler-detected pulmonary venous flow reversal:

a. is highly sensitive for severe mitral regurgitation.
b. is highly specific for severe mitral regurgitation.
c. is unrelated to mitral regurgitation severity.
d. helps separate organic from functional mitral regurgitation.

Hirudin for Acute Coronary Syndromes

ABSTRACT & COMMENTARY

Synopsis: *Hirudin is superior to heparin for preventing cardiac events in the first week after the onset of an acute coronary syndrome.*

Source: Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. *Lancet* 1999; 353:429-438.

The organisation to assess strategies for Ischemic Syndromes (OASIS) conducted a pilot trial of patients with unstable angina or non-Q-wave myocardial infarction (MI) and found that hirudin reduced cardiac events over seven days. Thus, a longer study was carried out that compared hirudin to heparin. All 10,141 patients took aspirin and were randomized to standard-dose heparin or medium-dose hirudin (0.4 mg/kg bolus, then 0.15 mg/kg/h infusion) for 72 hours. The primary end point was cardiovascular death or new MI within seven days. The primary end point occurred in 4.2% of the heparin group and 3.6% of the hirudin group (relative risk [RR], 0.84; P = 0.08). If refractory angina is combined with the primary end points, the event was 6.7% with heparin and 5.6% with hirudin (RR, 0.82; P = 0.02). These differences were largely observed during the 72-hour treatment period. More patients in the hirudin group vs. the heparin group had treatment stopped early due to excess bleeding or other adverse events (2.8% vs 1.3%; P < 0.001) and more had major bleeding episodes in general (1.2 vs 0.7%; P = 0.01). Almost all these were in the first 72 hours and due to gastrointestinal bleeding. The incidence of stroke was similar and there was only one hemorrhagic stroke, which occurred in the heparin group. The OASIS investigators conclude that hirudin is superior to heparin for preventing cardiac events in the first week after the onset of an acute coronary syndrome.

COMMENT BY MICHAEL H. CRAWFORD, MD

Unstable angina/non-Q-wave MI remains a common cause for hospital admission, and, despite modern aggressive therapy, 10-15% suffer Q-wave MI or need urgent revascularization for refractory symptoms. Despite these undesirable outcomes, both the TIMI III and VANQWISH trials showed little benefit from an aggressive early revascularization approach. Thus, there has been considerable interest in new pharmacological approaches that more adequately attack the underlying pathophysiology. Platelet IIb/IIIa inhibitors have shown some promise, but the studies have shown inconsistent results vs. heparin therapy. However, the GUSTO IIb, TIMI 9B, and OASIS I studies have exhibited consistent moderate gains of hirudin over heparin therapy. Since most patients with unstable angina receive a cocktail of five or more drugs, the ability of any new drug to affect "standard therapy" is problematic. Remarkably, hirudin showed an approximately 20% decrease in ischemic events in this robust trial.

The rationale for the improved outcomes with hirudin

is that it is a direct thrombin inhibitor, whereas heparin is an indirect inhibitor. The hirudin used in this study (lepirudin, Hoechst Marion Roussel, Germany) is a recombinant DNA product derived from the medicinal leech. It inhibits both clot-bound and circulating thrombin. Thus, it is probably not surprising that major and minor bleeding episodes were more common with hirudin, but there was no increase in life-threatening bleeds. Overall, the rate of major bleeding complications was low in this trial (< 2%). This is probably because the rate of percutaneous and surgical revascularization was low (6-7%). In a more aggressively managed patient group, bleeding complications could be more profound.

Cardiac events still occur beyond seven days from the onset of unstable angina despite aspirin and other therapies. For this reason, the investigators in OASIS II are conducting a substudy of long-term warfarin. Also, the issue of continuing hirudin for more than 72 hours, an oral IIb/IIIa agent, or subcutaneous low-molecular-weight heparin for more than seven days should be considered. Clearly, the optimal treatment of unstable angina is unknown, but the pharmacologic possibilities are widening and hirudin appears to be a strong contender to replace intravenous heparin. ❖

The OASIS-II study showed that hirudin vs. heparin in acute coronary syndromes:

a. significantly reduced cardiovascular deaths.
b. significantly reduced CV death and myocardial infarction.
c. significantly reduced CV death, MI or refractory angina.
d. None of the above

Multicenter Clinical Trial of Catheter Ablation

ABSTRACT & COMMENTARY

Synopsis: *Between 1992 and 1995, catheter ablation had matured to be a standard procedure with a high success rate and an acceptable risk.*

Source: Calkins H, et al. For the Atakr Multicenter Investigators Group. *Circulation* 1999;99:262-270.

In this report, calkins and colleagues report the results of catheter ablation procedures during a large multicenter study performed during the clinical investigation of a new temperature-controlled ablation system. The studies were performed at 18 adult and pediatric institutions between 1992 and 1995. A total of 1136 ablation procedures were performed in 1050 patients. As part of the investigational protocol to test the efficacy and complications associated with this ablation system, Calkins et al tabulated clinical variables, success rates, arrhythmia recurrence rates after the procedure, and early and late complications.

The patient population consisted of 489 males and 561 females with a mean age of 37 ± 18 years. Among the entire group, 13% were younger than 13 years of age and an additional 18% were between 13 and 20 years of age. Five hundred patients underwent ablation of a single accessory pathway, 373 underwent ablation for AV node reentrant tachycardia, and 121 underwent ablation of the AV junction. An additional 56 patients had more than one type of ablation procedure. In keeping with the natural history of these disorders, patients who underwent ablation of an accessory pathway were younger than patients with AV node reentrant tachycardia, who, in turn, were younger than those who underwent ablation of the AV junction. Catheter ablation was successful in 95% of the patients. Two ablation sessions were required in 42 patients. Second ablation sessions were more commonly required in patients with right free wall or posteroseptal accessory pathways and in patients with either multiple accessory pathways or multiple targets. There was a higher success rate with ablation of left free wall accessory pathways (95%) compared to right free wall and posteroseptal accessory pathways (90% and 80%, respectively).

Major complications occurred within one month of the ablation procedure in 32 (3%) patients, with minor complications noted in an additional 87 patients. There were three patient deaths, two strokes, one myocardial infarction, 10 cases of inadvertent complete AV block, and six cases of tamponade. The three deaths were due to dissection of a coronary artery, ventricular fibrillation seven days after AV junctional ablation, and an apparent

The Physician's Therapeutics & Drug Alert

The publishers of *Clinical Cardiology Alert* invite you to try a risk-free subscription to *The Physician's Therapeutics & Drug Alert.* Edited by William T. Elliott, MD, this monthly publication brings you the latest information on new pharmacologic treatments, new indications for existing drugs, and recent FDA approvals. It also provides the opportunity for you to earn up to 20 hours of CME credit per year.
Annual subscription price: $99. For more information or to order, please call our Customer Service department at **1-800-688-2421.**

pulmonary embolus 14 days after AV junctional ablation. The three predictors of a major complication were: increased patient age, the presence of structural heart disease, and the presence of multiple ablation targets.

Echocardiograms were performed before and after catheter ablation in 972 patients. In addition to the six patients who developed clinical evidence of tamponade, an additional 20 patients had pericardial effusions after the procedures. Although some changes in valvular regurgitation were noted, these were felt not to be directly due to the ablation procedure itself.

After an initially successful ablation procedure, 6% of the patients developed recurrent arrhythmias. Recurrence was more common among patients who had undergone ablation of an accessory pathway (7.8%) compared to those who had undergone ablation for AV nodal reentrant tachycardia (4.6%) or those who had undergone ablation of the AV junction (1.9%). Recurrence was more common with septal, posteroseptal, or right free wall accessory pathways and in patients who had multiple accessory pathways.

During long-term follow-up, there were 23 deaths. Of these, five were classified as sudden cardiac death and one was due to a pulmonary embolus that was presumed to be a late complication of the procedure. The four predictors of death were patient age, the presence of structural heart disease, a lower ejection fraction, and AV junctional ablation.

Calkins et al conclude that between 1992 and 1995, catheter ablation had matured to be a standard procedure with a high success rate and an acceptable risk. Their data may serve as a useful guide to clinicians considering therapeutic options for patients who have arrhythmias susceptible to catheter ablation.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Catheter ablation has progressed rapidly as a technique for managing arrhythmias since it was first introduced almost 20 years ago. Initially, DC shock was used to ablate the AV junction, posteroseptal accessory pathways, and ventricular tachycardia. The development of radiofrequency ablation made the procedure considerably more attractive and more than 20,000 radiofrequency ablation procedures are performed annually in the United States. Although previous reports on the success and complications of radiofrequency ablation have been published, they have either represented single laboratory reports or voluntary registry data. The latter likely underreport complications and the former may not represent the efficacy rate in usual practice. Few prior studies had extensive data about late recurrence. This study, since it involved the clinical trial of an investigational ablation system, provided a uniform method for data collection and follow-up and, therefore, represents probably the most accurate assessment of radiofrequency catheter ablation yet available.

The major limitation to this paper is that the data were obtained between 1992 and 1995. This period was still early in the learning curve for many centers. Calkins et al identified the number of procedures performed at a center as a predictor of success. By now, however, any large center should have performed hundreds of catheter ablation procedures, not just the number (40) that were associated with a higher rate of success in this study. However, as more electrophysiologists have been trained in this technique, many now practice in relatively low-volume centers and data about the number of procedures required to maintain a high level of success are not available. In addition, this paper does not include data about the success rates or complication rates for ablation of atrial tachycardias, ventricular tachycardias, atrial flutter, or atrial fibrillation. Ablation for these arrhythmias is often more complicated, and up-to-date data about the success and complications during ablation attempts with these arrhythmias would be valuable. ❖

Radiofrequency catheter ablation for supraventricular rhythm disturbances:

a. is successful 95% of the time.
b. has a 3% rate of major complications.
c. has a 6% arrhythmia recurrence rate.
d. All of the above

American Health Consultants introduces . . .

***Sports Medicine Reports*—The Essential Guide to Developments in Sports Medicine and Orthopaedics**

Never before have you seen advances in sports medicine and orthopaedics come this quickly. The way you treat a rotator cuff injury or torn knee ligaments will be obsolete in five years. With your multiple obligations, who has time to read every relevant journal article in depth? That's why you need a subscription to *Sports Medicine Reports*, edited by James D. Heckman, MD.

Keep informed about important clinical advances and earn 20 CME credits, free of charge.

Call our customer service department today at **1-800-688-2421** for more information or to subscribe.
Annual subscription price: $189 with 20 AMA Category 1 CME credits.