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CARDIOVASCULAR UPDATE

Clinical Cardiology and Cardiovascular Surgery News

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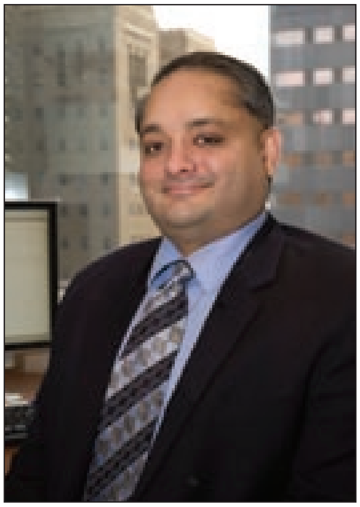
Inside This Issue

The Emerging Role of 3D Echocardiography



Sunil V. Mankad, MD

Three-dimensional (3D) echocardiography is one of several emerging modalities that have enhanced delineation of cardiac anatomy and function. This modality was first described in the 1960s, and the first real-time 3D echocardiographic scanner was developed in the early 1990s. However, early attempts were limited by relatively poor image quality and low frame-rates. More recently, the development of matrix-array transducers (incorporating more than 3,000 imaging elements compared with sparse-array transducers, which used 256 imaging elements) has transformed 3D echocardiography by offering markedly improved image resolution. Further refinements have resulted in a smaller transducer "footprint," less artifact, and better penetration and have also incorporated harmonic imaging. With any novel imaging modality, however, enthusiasm to embrace its use must be tempered with an understanding of its limitations.

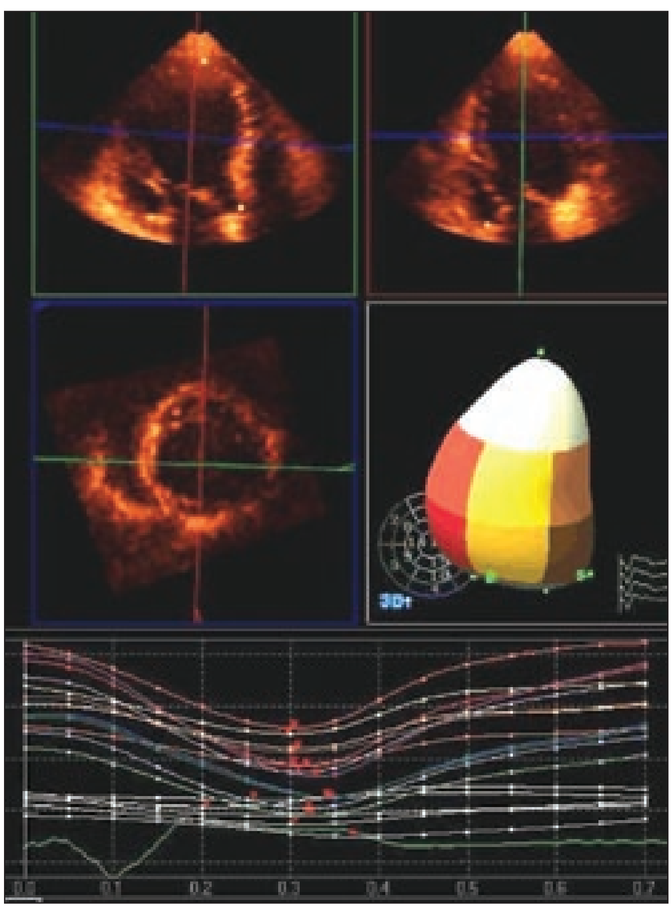


Figure 1. 3D Echocardiography for Global and Regional LV Systolic Function. The top 4 images are representative B-mode echocardiographic images used in the multi-planar reconstruction of the left ventricle (LV) for 3D calculation of volumes and ejection fraction. Regional LV volumes are divided up in the American Society of Echocardiography 17-segment model. Below these images are the time-volume curves (change in volume) for each individual LV volume segment.

Assessment of Ventricular Function

The assessment of ventricular function remains the most common reason for echocardiography. Even when ventricular function is not the focus of the examination, its assessment often is critical to clinical decision making. While 2D echocardiography does provide an accurate method for the assessment of left ventricular (LV) systolic function, the geometric assumptions used to calculate ejection fraction (EF) are less robust when regional wall motion abnormalities are present, creating asymmetric ventricular contraction. 3D echocardiography provides greater reproducibility, reliability, and accuracy than 2D echocardiography in the assessment of LV volumes and EF compared with gold standards such as cardiac MRI or radionuclide volumes. This difference becomes even more pronounced when asymmetric ventricles are evaluated. 3D echocardiography captures the entire LV volume, and images can be displayed in multiple orientations. Global as well as regional wall motion can be displayed parametrically (Figure 1).

In the past, image acquisition required data to be captured over multiple cardiac cycles. This can be problematic in patients with cardiac arrhythmias or those in whom breath-hold imaging is not possible, leading to the creation of considerable imaging artifact. However, single-beat acquisition will soon be available and will overcome this limitation. Preliminary data have confirmed the feasibility and potential clinical utility of 3D echocardiography in stress echocardiography although image quality remains a

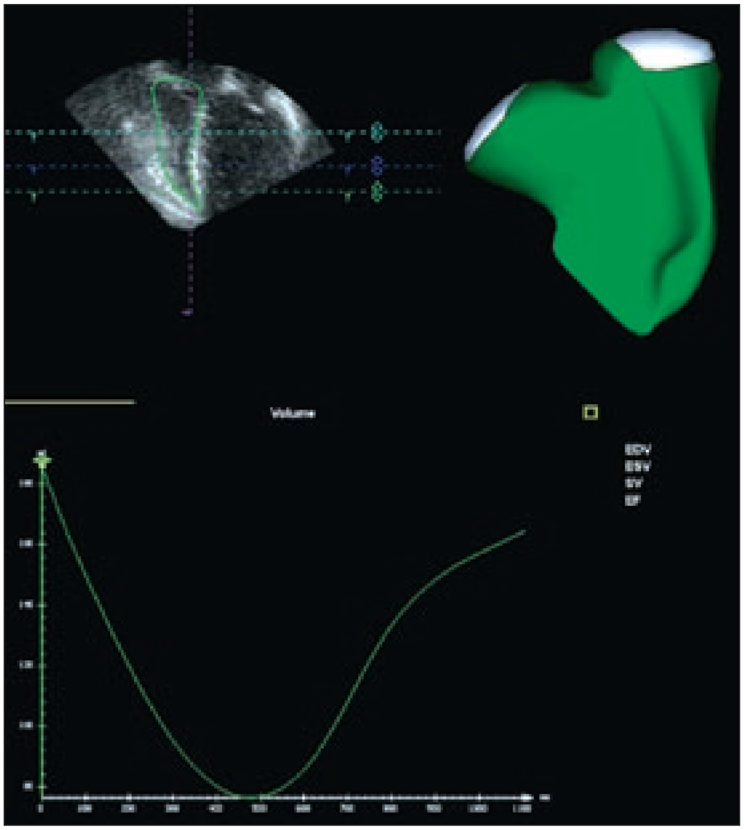


Figure 2. 3D Echocardiography for RV Volumes and Systolic Function. Top left, A single-slice 2D echo cut through the right ventricle (RV) with a representative endocardial trace generated by automatic contour tracking software once multiple key right heart landmarks are identified and marked. Top right, The 3D representation of the RV made by stacking multiple 2D echo slices similar to the figure at left (individual slices are tracked, not predicted by any geometric assumptions). Below these images is the time-volume curve for the right ventricle.

concern. The important advantage of 3D echocardiography in the stress setting is that data can be obtained using only 1 or 2 imaging windows without the need for transducer movement, thus reducing imaging time.

The asymmetric and pyramidal shape of the right ventricle (RV) has limited the ability to calculate EF of this chamber using 2D echocardiography. Recently, several centers, including Mayo Clinic in Rochester, have demonstrated the feasibility of using 3D echocardiography and novel offline tracking software to calculate RV EF and volumes accurately. Not only does this technique allow for better assessment of RV function, but in many instances, RV stroke volume can be incorporated into the continuity equation to facilitate left-sided valve regurgitation calculations. An example of 3D echocardiographic assessment of RV EF and volumes is shown in Figure 2.

Congenital Heart Disease

The unique perspectives and versatility that 3D echocardiography provides may also be of value in the assessment of congenital cardiac lesions. The superior ability to display the complex but pivotal spatial relationships using 3D echocardiography has been described in multiple case reports. An example of an ostium secundum atrial septal defect shown from the right atrial perspective is shown in Figure 3. The defect's true rim, actual size, surrounding structures, and shape are well delineated. Future studies are needed to clarify the impact of 3D echocardiography in the operative repair of various congenital heart lesions.

LV Dyssynchrony

To date, the assessment of LV dyssynchrony using 2D and Doppler techniques has been disappointing. Unlike 2D echocardiography, which relies heavily on geometric assumptions to provide quantitative parameters of LV function, 3D echocardiography can simultaneously integrate the effects of radial, circumferential, and longitudinal contraction of all 17 myocardial segments on cardiac dyssynchrony. A semiautomated detection process, through endocardial traces of 2D subsections of the full-volume data, can be used to generate a mathematically based "cast" of the LV cavity that provides time-volume data for the entire cardiac cycle. These time-volume data are subsequently divided into time-volume estimates for each of the 17 standard segments. Single-center studies have demonstrated the calculation of a systolic dyssynchrony index, using a standard deviation of the time to minimum regional volume for each segment normalized as a percentage of the duration of the cardiac cycle. An example of severe LV dyssynchrony demonstrated by 3D echocardiography and a marked response, including considerable reverse remodeling with cardiac resynchronization therapy, is shown in Figure 4. Technical difficulties with capturing the entire LV volume in a single data set in patients with markedly dilated hearts remain a concern, and large-scale clinical validation trials are needed before 3D echocardiography should be considered for clinical use in these patients.

Conclusions

3D echocardiography is an emerging modality with a diverse array of clinical applications, including assessment of biventricular volumes and systolic function, congenital heart disease, and LV dyssynchrony. It complements current 2D echocardiographic techniques, and its use continues to evolve as technologic advances emerge. The role of 3D echocardiography will be discussed further in an upcoming issue of *Cardiovascular Update* devoted to valvular heart disease.

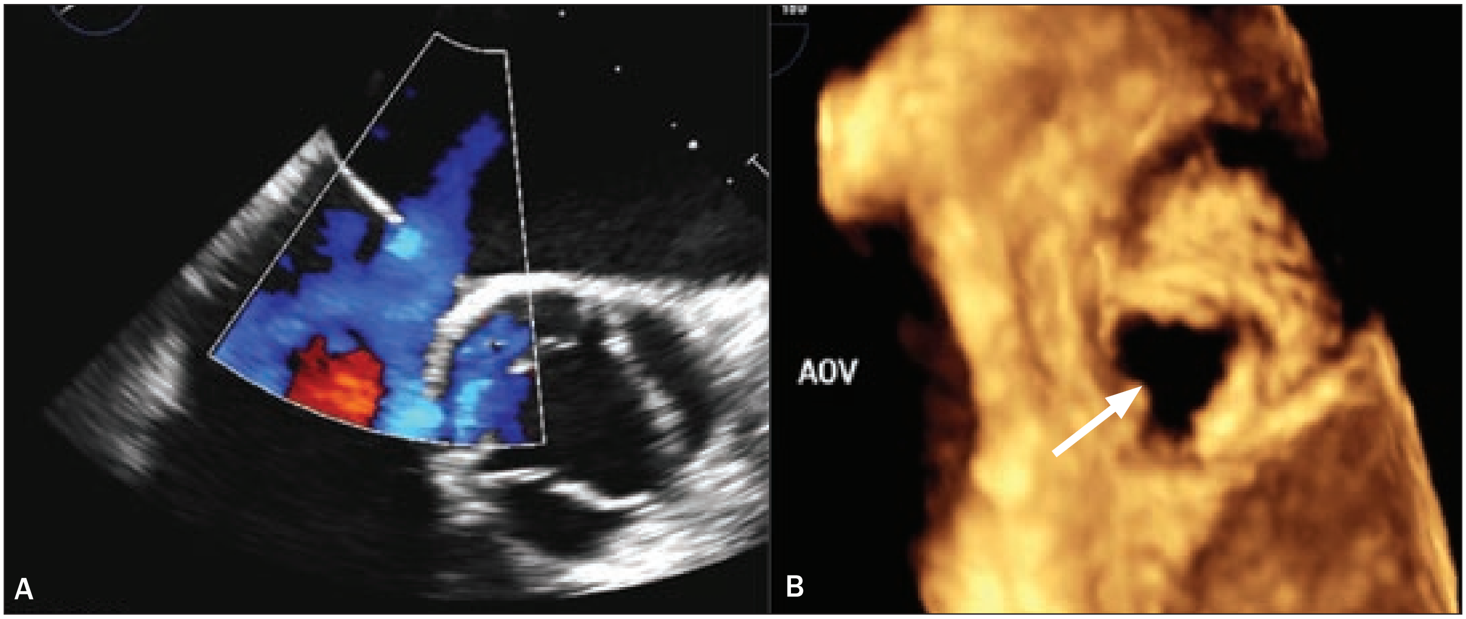


Figure 3. Ostium Secundum Atrial Septal Defect. A, 2D transesophageal echocardiographic image in a patient with an ostium secundum atrial septal defect; the defect is well seen with color Doppler indicating left to right flow. B, 3D echocardiographic en face image from the right atrial perspective gives a clearer picture of the true size, shape, and rim of the defect (arrow). This information can be useful in planning closure. AOV, aortic valve.

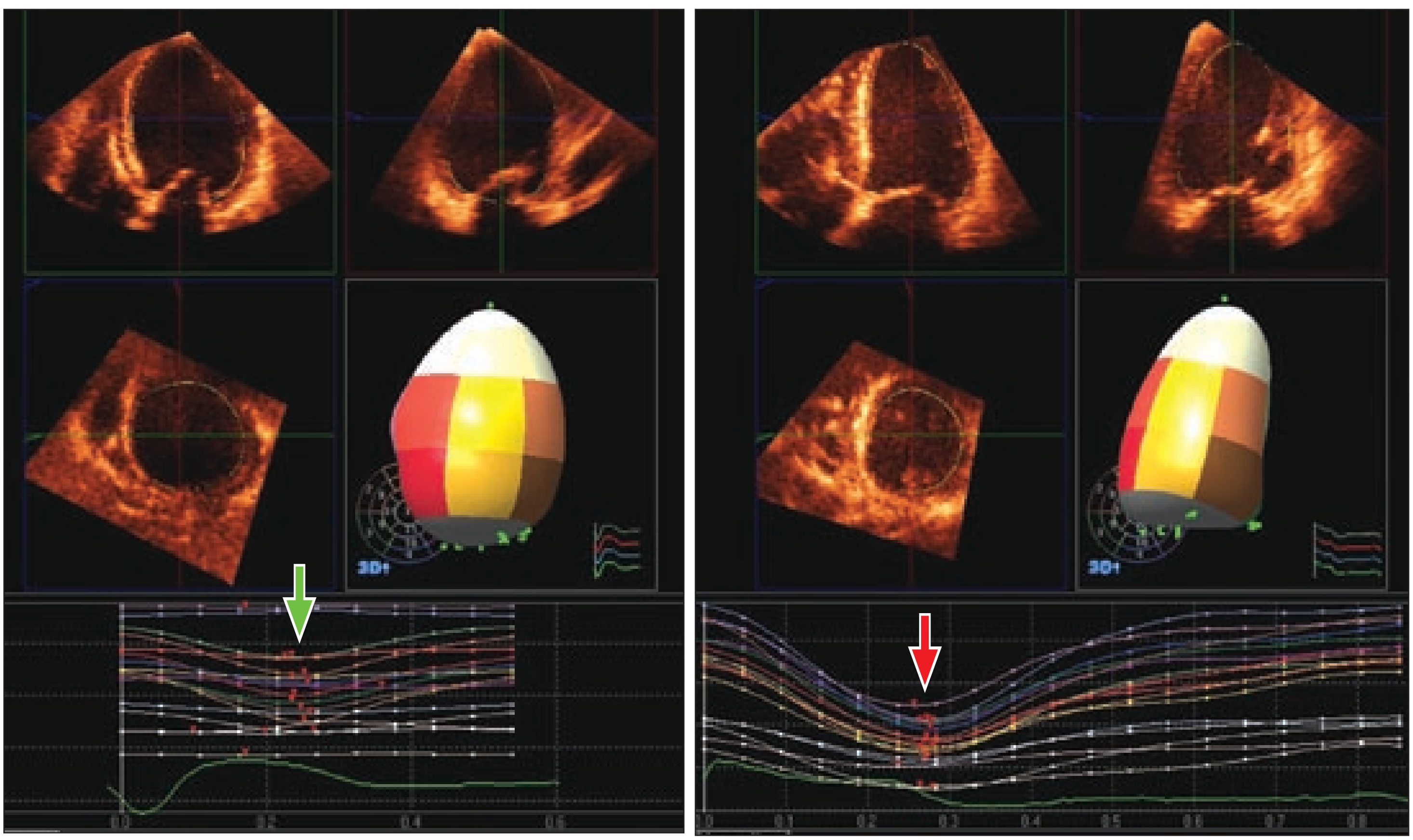


Figure 4. 3D Echocardiography for Left Ventricular Dyssynchrony. Segmental volume curves before (left) and 12 months after (right) cardiac resynchronization therapy (CRT) in an 81-year-old woman with nonischemic dilated cardiomyopathy who underwent the upgrade from a dual-chamber pacemaker to a biventricular pacemaker. The standard deviation in time to minimal volume in 16 segments improved from 8.1% (green arrow) to 1.1% (red arrow) after CRT. This patient showed considerable reverse remodeling at 12 months after CRT (end-systolic volume, 197 mL to 47 mL; end-diastolic volume, 226 mL to 104 mL) (image courtesy of Chinami Miyazaki, MD).

Recent JUPITER Trial Results Suggest Expanded Role for Statin Drugs

Steven L. Kopecky, MD

The JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study, recently published in the *New England Journal of Medicine* (359(21):2195-2207, November 20, 2008) and presented at the American Heart Association annual meeting has raised questions about the role of statin drugs in the primary prevention of cardiovascular disease. The JUPITER study enrolled almost 18,000 patients to receive either rosuvastatin (Crestor), 20 mg daily, or placebo. All patients had a C-reactive protein (CRP) level higher than 2 mg/L at baseline; the mean LDL at baseline was 108 mg/dL and was reduced to 55 mg/dL in those patients treated with rosuvastatin. The study was stopped early at 1.9 years by its Data Safety Monitoring Committee because of the beneficial results.

What were those beneficial results?

"The primary end point, which was reduced by almost 50% during the study, was nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death," according to Stephen L. Kopecky, MD, a cardiologist in the Cardiovascular Health Clinic at Mayo Clinic in Rochester. The "number needed to treat" during the 1.9-year treatment period was approximately 120 patients to prevent 1 primary event.

As stated above, all patients had an elevated CRP at baseline, but they did not have evidence of overt cardiovascular disease or of hypertension. However, these patients did have other risk factors: 15% were smokers, 11% had a family history of coronary artery disease, and 41% had metabolic syndrome. Patients with isolated elevated CRP (no tobacco abuse, normal weight, no metabolic syndrome, Framingham risk score less than 10% at 10 years, and LDL less than 100 mg/dL) were evaluated in a subgroup analysis; these patients also benefited by similar extent.

What about adverse events?

The incidence of liver function test abnormalities and muscle weakness was similar in the placebo group and the rosuvastatin group. Also, although there was no significant difference in blood glucose or hemoglobin A1c levels in the treated group compared with the placebo group, the treated group had a higher incidence of diabetes; for every 200 patients treated, an extra case of diabetes was diagnosed.

What about the cost?

The cost of saving 1 life with rosuvastatin was $480,000 vs $24,000 with use of a generic statin.

Was this a test of the elevated CRP–elevated risk hypothesis?

No, because all patients had a high CRP level. To answer the questions of whether elevated CRP levels predict risk of cardiovascular disease and whether treatment that lowers CRP levels also lowers cardiovascular risk would require a study with 2 groups of similar patients with the only difference between the groups being high vs normal CRP. It is possible that in the JUPITER study the CRP elevation was present only because of concomitant factors such as tobacco use, metabolic syndrome, obesity, or genetic differences.

Will these study results change practice?

In the Cardiovascular Health Clinic at Mayo Clinic in Rochester, the recommended goal for LDL follows the American Heart Association/American College of Cardiology guideline—LDL should be less than 70 mg/dL in all patients with known coronary disease. "We have also recommended a target LDL of less than 70 mg/dL in all patients who have evidence of subclinical coronary artery disease such as coronary artery calcification, peripheral artery disease, or diabetes," says Dr Kopecky. For patients without overt or subclinical cardiovascular disease, it is recommended that they discontinue smoking, eat at least 5 fruits or vegetables per day, try to reduce body mass index to approximately 25, and exercise vigorously at least 150 to 200 minutes per week, especially if their LDL is higher than 130 mg/dL. The JUPITER study results suggest that lower LDL levels are optimal, even in patients with seemingly minimal risk factors. The independent role of elevated CRP in the risk of cardiovascular disease remains unanswered.

Cardiologists Critical to Integrated Management of Peripheral Artery Disease

Rajiv Gulati, MD, and Verghese Mathew, MD

Peripheral artery disease (PAD) currently affects between 8 million and 12 million people in the United States, and its prevalence will likely reach 20 million in 10 years. Although 70% of patients may be asymptomatic at any given time, the presence of PAD is a powerful predictor of early morbidity and mortality. The poor prognosis of PAD (disease affecting any of upper or lower extremity, renal and mesenteric arteries) confers a markedly increased risk of subsequent ischemic cardiac and cerebrovascular events, reflecting the coexistence of often asymptomatic coronary and carotid disease. Even a mildly reduced ankle brachial index (ABI) of less than 0.9 (ratio of ankle to brachial systolic blood pressures), reflecting mildly obstructive disease, confers a markedly increased risk of subsequent myocardial infarction, congestive heart failure, transient ischemic attack, stroke, and death. The presence of asymptomatic PAD should therefore provide motivation for both patients and clinicians to aggressively reduce risk factors in an attempt to limit cardiovascular morbidity and mortality. Conversely, the presence of coronary or carotid disease should alert the physician to consider the coexistence of PAD (Figure 1).

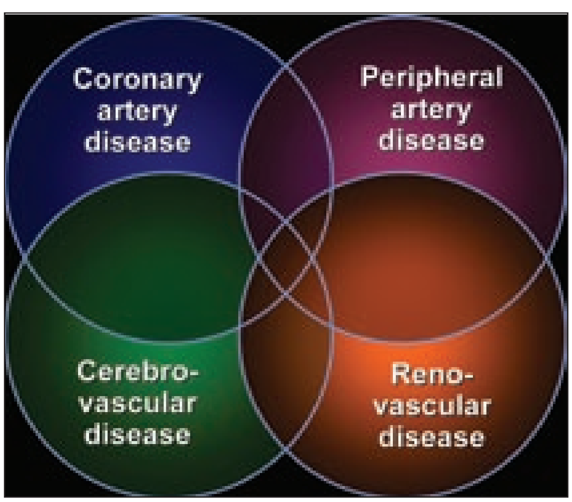


Figure 1. Atherosclerotic artery disease, a global problem.

The Role of Cardiologists in a Global Vascular Approach

In addition to being aware of the systemic nature of atherosclerosis and the strong association between coronary and peripheral artery disease, specific peripheral vascular disorders may affect the management of cardiac disease. Renal artery stenosis (RAS) is the most common secondary cause of hypertension in patients with atherosclerosis. Moreover, renovascular hypertension is often resistant to medical therapy, thus increasing cardiovascular risk. "Bilateral RAS may produce flash pulmonary edema in patients with normal left ventricular function," according to Verghese Mathew, MD, an interventional cardiologist at Mayo Clinic in Rochester. Subclavian artery stenosis may lead to angina or even myocardial infarction by compromising inflow to left or right internal mammary bypass grafts. Claudication from lower extremity artery disease may limit mobilization and impair the effectiveness of cardiac rehabilitation programs. Iliac and subclavian artery stenoses may limit access for cardiac catheterization and percutaneous coronary intervention.

Situations such as these have led to an increasing role for cardiologists not only in the recognition and medical management of global vascular disease but also in therapeutic endovascular approaches for noncoronary revascularization. Mayo Clinic in Rochester has adopted an integrated treatment approach with formation of the Gonda Vascular Center, which brings together endovascular specialists from vascular medicine, vascular radiology, vascular surgery, and interventional cardiology. The notable overlap of incidence, natural history, and treatment outcomes between coronary and noncoronary atherosclerosis highlights the importance of cardiologists' participation in an integrated practice.

A full range of adjunctive, specialist diagnostic, and therapeutic devices are available in the cardiac endovascular suite, for example:

- Pressure wires with a built-in pressure sensor at the tip to measure translesional peripheral and renal artery gradients and determine hemodynamic importance.
- Intravascular ultrasound for lesion assessment and for optimization after angioplasty or stenting.
- Specific atherectomy devices to debulk, slice, and remove plaque through long segments of heavily calcified lesions.
- Excimer laser technology for endovascular ablation of total occlusions.

- Reentry catheters designed specifically to guide wire reentry into the distal true lumen after the deliberate crossing of a total occlusion through a subintimal false channel.
- Stereotaxis, the use of a large external magnet to accurately and incrementally deflect a magnetized wire tip, to facilitate passage of the wire into heavily angulated segments that would otherwise be unapproachable in a traditional endovascular manner.

Claudication

The mainstay of therapy consists of risk factor modification in conjunction with antiplatelet therapy. A supervised exercise program and pharmacologic therapy with phosphodiesterase inhibitors have additional proven benefit. Revascularization has typically been reserved for patients with persistent lifestyle limitations. However, studies to address whether early endovascular intervention may modify the subsequent clinical course are ongoing and may have widespread implications. "The impact of revascularization modalities has traditionally been measured in terms of mortality, major morbidity, and limb loss," says Rajiv Gulati, MD, PhD, an interventional cardiologist at Mayo Clinic in Rochester. "Quality-of-life metrics are now increasingly recognized as important end points, given the impact of limb pain and reduced function on daily activities, physical rehabilitation, and ability to maintain employment," he says.

The past few years have seen a dramatic shift toward an endovascular rather than a surgical approach for revascularization of occlusive lower extremity artery disease. Overall, the number of patients undergoing endovascular revascularization has increased. Patients who previously were considered too high risk for surgery are now eligible for percutaneous approaches, with rapid recovery time and reduced morbidity. American Heart Association/American College of Cardiology guidelines designate a class 1 indication for endovascular revascularization for limiting claudication and either 1) failure of conservative measures and/or 2) favorable risk-benefit ratio, eg, focal aortoiliac disease. The latter, suggesting that earlier intervention is reasonable even without an attempt at conservative measures, is based on the well-established success rates and sustained durability of stenting for aortoiliac level disease.

"In patients with severe obstructive disease or occlusions throughout a limb, very often treatment of proximal level stenoses alone, for example, at the iliac or femoral level, will cure or markedly reduce claudication symptoms, despite residual high-grade occlusive disease more distally," says Gregory W. Barsness, MD, an interventional cardiologist at Mayo Clinic in Rochester. In other circumstances of complex disease patterns, a hybrid endovascular-surgical approach may be considered. An example might include unilateral common iliac stenting combined with femoral-to-femoral crossover grafting (a relatively low-risk surgical procedure), obviating the need for an abdominal incision and aortic graft. Endovascular intervention for symptomatic infrapopliteal disease is being increasingly undertaken for management of claudication. In contrast to aortoiliac disease, restenosis and reocclusion in the superficial femoral artery and distal vessels remain a serious problem; it is unknown whether the use of drug-eluting stents or drug-coated angioplasty balloons will limit restenosis.

TABLE

Clues to Renal Artery Stenosis

- Known atherosclerosis
- Onset of hypertension before the age of 30 years or after the age of 55 years
- Worsening of previously controlled hypertension
- Malignant or resistant hypertension
- Abdominal bruit
- Discrepancy of renal size
- Azotemia not otherwise explained or worsened by angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
- Recurrent congestive heart failure or flash pulmonary edema in a hypertensive patient, particularly with preserved systolic left ventricular function

Critical Limb Ischemia

The presence of rest pain, nonhealing ulcer, or gangrene may represent critical limb ischemia (CLI). The diagnosis can be strengthened by physical examination (ischemic tissue loss, absent pulses) and objective noninvasive evaluation (low ABI, weak Doppler signals, critically reduced transcutaneous PO_2). CLI is associated with 25% mortality and 50% limb loss at 1 year. "The optimal treatment is prompt revascularization, which can be surgical or endovascular," says Dr Gulati. The therapeutic goal is to reestablish single-vessel, in-line (uninterrupted) arterial flow to the foot. This often requires multiple level dilation and endovascular reconstruction of at least a single infrapopliteal vessel. In contrast to the management of stable claudication, endovascular treatment of proximal disease alone to optimize collateraliza-

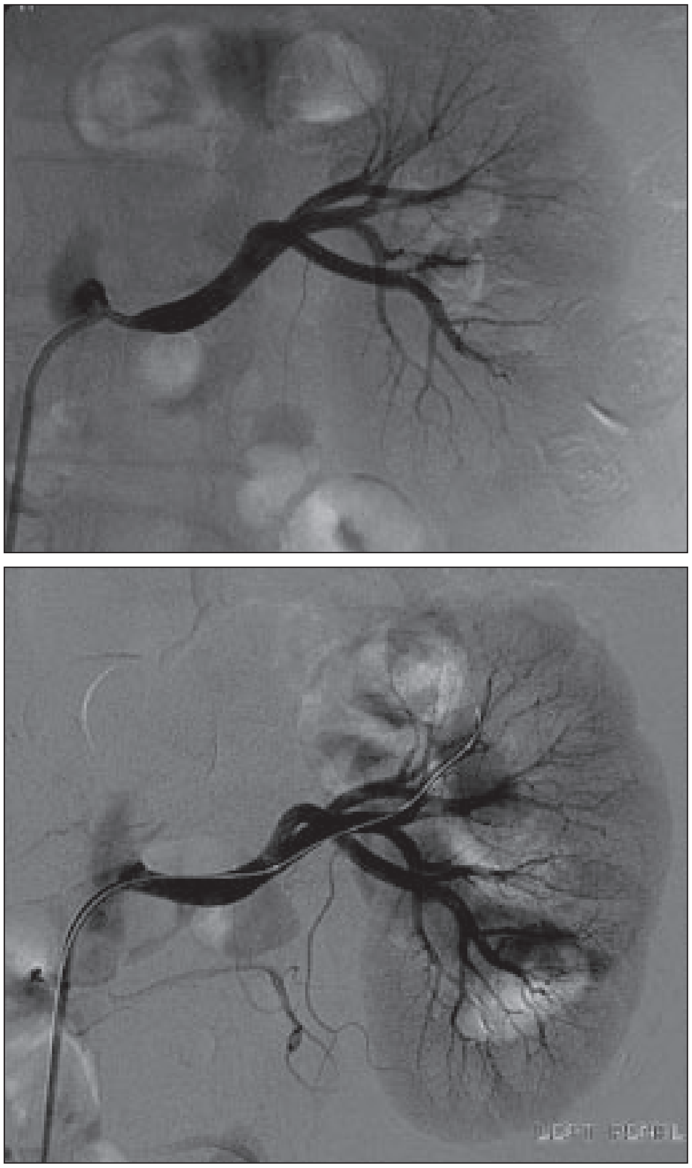


Figure 2. A 58-year-old woman presented with resistant, 5-agent hypertension; her serum creatinine had increased from 1.0 mg/dL to 2.0 mg/dL over the preceding year. Her hypertension had been well controlled on 2 agents 2 years earlier. Bilateral elevated renal artery velocities were identified on ultrasound with normal-sized renal arteries. Angiography, pressure wire assessment, and intravascular ultrasound confirmed physiologically important, high-grade stenoses bilaterally (top). Both renal arteries were dilated, and blood pressure control began to improve within 24 hours (bottom). At follow-up 1 month later, she had returned to 2 pharmacologic agents, and her creatinine level had normalized.

tion of occluded infrapopliteal vessels may not be sufficient for healing of distal extremity ulcers because of the supranormal metabolic requirements of the healing ulcer. However, in these circumstances, durability of patency after reconstruction may be of less concern than with claudication. "If patency is maintained for even a short period, wound healing and limb salvage can be achieved," says Dr Barsness.

Renal Artery Stenosis

The presence of atherosclerotic RAS is a risk factor for cardiovascular disease and is a strong predictor of mortality. RAS may lead to hypertension, deterioration of renal function, and irreversible renal tissue injury (ischemic nephropathy).

It can be difficult to determine whether the relationship between RAS and hypertension or renal impairment is causative (Table). Reliably defining patients who will benefit from revascularization remains a challenge. "The correlation of anatomic degree of stenosis with renal physiology and function is poor," says Dr Mathew. However, tools from the coronary arena are now increasingly used in the renal artery bed to address this concern. Renal lesions can now be comprehensively assessed for both stenosis severity and downstream end-organ impact (eg, measurement of translesional pressure gradient and flow reserve, flow quantification with a Doppler wire, determination of area of stenosis, and virtual histology evaluation by intravascular ultrasound). The use of these technologies will help refine the definition of physiologically relevant RAS to tailor revascularization for those patients with the greatest likelihood of benefit (Figure 2).

The incorporation of cardiac interventional techniques has expanded the armamentarium available in the treatment of these challenging patients. Further studies will help define appropriate timing and the optimal approach to disease in various vascular beds. For additional information or to refer a patient, please call 507-255-4244.

Do You Know?

Patients with urgent cardiovascular conditions are seen within 48 hours at Mayo Clinic in Rochester in divisions of cardiology, pediatric cardiology, and cardiovascular surgery.

Upcoming Courses

Continuing Medical Education, Mayo Clinic

To request additional information or to register, unless noted otherwise, please call 800-323-2688, e-mail cme@mayo.edu, or visit www.mayo.edu/cme.

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British Cardiovascular Society and Mayo Clinic Cardiology Review Course
Mar 2-6, 2009, London, England
Phone: 0207 383 3887; Web: www.bcs.com

Update on Women's Health
March 5-7, 2009, Scottsdale, AZ
Phone: 480-301-4580; e-mail: mcs.cme@mayo.edu

Clinical Reviews: A Primary Care and Internal Medicine Update
Mar 25-28, 2009, Scottsdale, AZ
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May 4-8, 2009, Rochester, MN

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Mayo Echocardiography Review Course for Boards and Recertification
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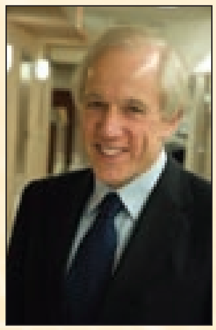
Mayo Interventional Cardiology Board Review
Oct 2-4, 2009, Rochester, MN

RECOGNITION



Stephen C. Hammill, MD (above left), received the Mayo Clinic Rochester Department of Medicine 2008 Henry S. Plummer Distinguished Physician Award. William T. Bardsley, MD (above right), received the Mayo Clinic Rochester Department of Medicine 2008 Laureate Award.

Raymond J. Gibbons, MD, received the Mayo Clinic Rochester Department of Medicine 2008 Outstanding Mentorship Award.

Mayo Cardiovascular Review Course for Cardiology Boards and Recertification
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Echocardiography in the Nation's Capital: Focus for the Sonographer
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