Doppler Helps Zero In on Diastolic Dysfunction

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NEW ORLEANS — A study that was unable to prove its primary hypothesis was still able to showcase a new way to assess diastolic dysfunction of the heart, a technique poised to help researchers explore new approaches to heart therapy.

"To our knowledge, this was the first study to demonstrate directly that blood pressure lowering can improve diastolic function, even in mildly hypertensive patients," said Dr. Scott D. Solomon, director of noninvasive cardiology at the Brigham and Women's Hospital in Boston.

The findings also suggest that "diastolic dysfunction is an early measure of end-organ damage and suggest a potential mechanistic link between hypertension and heart failure with preserved ejection fraction."

The technique used in the study is known as Doppler tissue imaging (DTI), which uses standard Doppler echocardiography hardware and software to directly measure myocardial relaxation velocity at the mitral anulus, a way to noninvasively assess diastolic dysfunction, Dr. Solomon said at the annual meeting of the American College of Cardiology. DTI already has a role for assessing patients with hypertension to determine whether high blood pressure has begun to impair heart relaxation, which can lead to diastolic dysfunction and heart failure.

"If a patient has a DTI abnormality and even mild hypertension, it makes me more aggressive [about reducing] blood-pressure," he said in an interview.

Most Doppler echocardiography units made in recent years can assess DTI. The most robust measure of DTI to gauge heart relaxation is E′ (E prime), the measure of the heart's early relaxation velocity. The study that Dr. Solomon reported at the meeting was designed to test whether blood pressure reduction using the angiotensin receptor blocker valsartan was especially effective for improving E′, compared with other antihypertensive drugs in patients with hypertension and an impaired relaxation velocity.

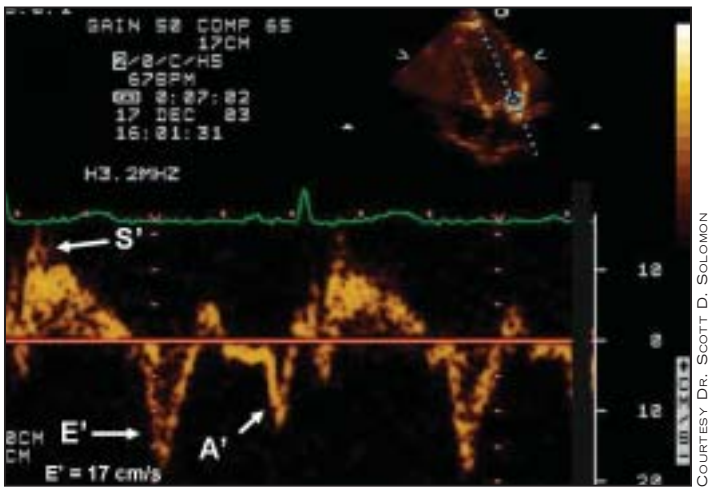
The underlying hypothesis was that a drug that reduces activation of the renin-angiotensin-aldosterone system (RAAS) would be more effective than other antihypertensive medications for reducing left ventricular hypertrophy and fibrosis and thereby improving diastolic function. The Valsartan in Diastolic Dysfunction study was sponsored by Novartis, which markets valsartan (Diovan). Dr. Solomon is a consultant to and has received honoraria from Novartis.

The study involved 384 patients aged 45 years or older with stage 1 or 2 hypertension, who also showed diastolic dysfunction based on their lateral E′ measure. The average E′ reading for all patients in the study was 7.5 cm/sec, substantially below the normal level for age (see box). The middle-aged patients had an average E′ level comparable with that of a 76-year-old person with no history of hypertension, Dr. Solomon said. Their average blood pressure at entry was about 144/86 mm Hg, and their average left ventricular ejection fraction was about 57%. About 4% of the participants had left ventricular hypertrophy.

The patients were randomized to two different antihypertensive regimens. One group received as its primary drug 320 mg/day of valsartan, followed by other, non–RAAS-affecting drugs as needed to reach a goal blood pressure of less than 135/80 mm Hg. The second group had the same goal blood pressure but did not receive any drugs that affect the RAAS. Alternative agents were used in this order: a diuretic, β-blocker, calcium channel blocker, and α-blocker. The control patients received significantly more antihypertensive medications, especially diuretics and calcium channel blockers.

After 9 months of treatment, the average blood pressure was 129/78 mm Hg in the patients treated with valsartan, and an average of 134/82 in the patients who did not get an RAAS-active drug. Follow-up DTI data were available for 341 patients. The study's primary end point was an improvement in the E′ measure, which rose by an average of 0.60 cm/sec in patients treated with valsartan and by an average of 0.44 cm/sec in the control patients. The difference between average improvements in the two groups was not statistically significant. But E′ was significantly improved over baseline levels in both groups, indicating that lowering blood pressure improves diastolic function.

The two groups did show a significant difference in two secondary efficacy measures made using DTI. Both the isovolumic relaxation time and the systolic contraction velocity showed improvements that were significantly greater in the valsartan group, compared with the control patients. ■



COURTESY DR. SCOTT D. SOLOMON

A DTI echocardiogram shows an early-relaxation velocity (E′) of 17 cm/sec, an indication of normal diastolic function.

Normal Heart Relaxation Velocity

Age (years)	E′
45-55	≥10 cm/sec
56-65	≥9 cm/sec
66-75	≥8 cm/sec

Note: Patients with an E′ that is below these age-specific levels have diastolic dysfunction.
Source: Dr. Solomon

ELSEVIER GLOBAL MEDICAL NEWS

Rosuvastatin Slows Carotid Atherosclerosis in Low-Risk Patients

BY MARY ANN MOON
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NEW ORLEANS — Rosuvastatin slowed the progression of carotid intima-media thickness in asymptomatic subjects at low risk of cardiovascular events but who nonetheless had subclinical atherosclerosis, Dr. John R. Crouse III reported at a conference sponsored by the American College of Cardiology.

The agent "basically halted progression" of intima-media thickness, Dr. Crouse said during a late-breaking clinical trials session at the meeting.

Unlike previous clinical trials of the drug involving high-risk subjects or patients with known cardiovascular disease, the METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) trial assessed asymptomatic people aged 45-70 years who were at low cardiovascular risk and had only moderately elevated cholesterol, but were found to have a relatively high carotid wall thickness on ultrasound examination.

The low-risk population was intentionally chosen for the study so that a placebo arm could ethically be included, said Dr. Crouse, professor of medicine and public health sciences at Wake Forest University in Winston-Salem, N.C.

A total of 984 subjects were enrolled in the study in August 2002–March 2004 at 61 medical centers in the United States and Europe and were followed with serial carotid imaging for 2 years. The study was funded by AstraZeneca Pharmaceuticals LP, maker of rosuvastatin (Crestor).

Ultrasound measurements of carotid intima-media thickness were performed at enrollment and at 6-month intervals for 2 years. Measurements were made at 12 carotid artery sites in each patient, including the near and far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery.

Results were available for 252 subjects who had been randomly assigned to receive placebo and 624 who had been assigned to receive 40 mg of rosuvastatin daily. This is not the recommended starting dosage but was selected "to provide the maximum efficacy expected to slow or delay progression of atherosclerosis," Dr. Crouse wrote in a report that was published at the time of the presentation (JAMA 2007;297:1344-53).

Carotid intima-media thickness progressed in the placebo group. It regressed in the rosuvastatin group, but the difference from baseline did not reach significance except at the common carotid artery.

The significant difference in progression between the placebo and rosuvastatin groups persisted across all clinical subgroups, regardless of subject age, sex, geographical location, race, body mass index, risk factors, blood pressure levels, or lipid levels, Dr. Crouse said.

Rosuvastatin did not induce regression of carotid atherosclerosis, as it has been shown to do in previous studies involving patients with more advanced disease. "This was focused on low-risk participants without advanced atherosclerosis, and this may have limited the opportunity to achieve disease regression," Dr. Crouse said.

LDL cholesterol declined by 49% and HDL cholesterol increased by 8% in patients taking rosuvastatin during the 2-year study. The frequency of adverse events was similar between the two groups, and most were of mild or moderate severity. Myalgia was the most commonly reported adverse effect.

In an editorial comment accompanying the published report, Dr. Michael S. Lauer of the Cleveland Clinic Heart Center said, "At first glance, the METEOR findings suggest there may be a role for routine arterial imaging" in low-risk people, and that routine rosuvastatin therapy may be warranted for those found to have increased carotid intima-media thickness.

But this would be "a radically different approach to primary prevention than that recommended by current guidelines," and the results clearly do not justify such a change, he said (JAMA 2007;297:1376-8).

For one thing, carotid intima-media thickness is merely a surrogate end point for clinical events, and the medical literature is rife with "numerous bad experiences whereby agents that improved surrogate end points yielded no benefit or were even found to cause harm when tested for their ability to prevent clinical events. Classic examples of this include vitamin E and postmenopausal hormone therapy," he wrote.

Moreover, there is only limited evidence that statin-induced changes in carotid intima-media thickness actually correlate with a decrease in atherosclerotic events.

The METEOR study had two additional weaknesses. "A fair number of enrolled patients failed to complete the protocol and were lost to follow-up. …[A] higher rate of follow-up clearly would have increased the credibility of the findings," he noted.

And the study was not powered to evaluate the drug's effect on clinical events. In nearly 1,000 subjects, only six ischemic events occurred—all of them, "curiously," in subjects taking the study drug. "Ambitious event-based randomized trials involving large numbers of patients and communities must be done," Dr. Lauer said. ■