

Improved Cardiac Monitoring Tracks Adult CHD

BY JANE SALODOF MACNEIL
Southwest Bureau

SCOTTSDALE, ARIZ. — With many more infants surviving congenital heart disease, pediatric cardiologists have a new challenge, Dr. Alan H. Friedman told physicians at a pediatric update sponsored by Phoenix Children's Hospital.

Many more survivors must be followed through adolescence and into adulthood with noninvasive cardiac monitoring, said Dr. Friedman, director of pediatric cardiovascular imaging services at Yale–New Haven (Conn.) Children's Hospital, and of Yale University, New Haven.

Four-dimensional magnetic resonance imaging is “where the future of cardiology is going to be,” he predicted. It is safer than methods that expose them to radiation, and it has the potential to provide more graphic information than can be obtained with any other technology.

“The future will be to take three-dimensional imaging in time and rotate it so



‘This is not a competition between these different imaging technologies ... they complement each other.’

DR. FRIEDMAN

we can provide to our surgeons the most graphic information,” he said.

In the meantime, new and better tools have already expanded the physician's ability to image the heart and other structures within small pediatric patients.

“This is not a competition between these different imaging technologies, but rather that they complement each other,” he said, comparing the options.

The chest x-ray remains a part of everyday practice, he said, praising its accuracy in depicting the relationship between the heart and lungs: in particular, cardiac size, pulmonary blood flow, and pulmonary edema. Radiation exposure is minimal with chest x-rays, he continued. But they are not specific enough to assess certain forms of congenital heart disease (CHD).

Dr. Friedman described ultrasound as the workhorse of pediatric cardiology. Transthoracic echocardiography is safe and portable with the use of laptops that can be brought directly to the bedside.

Echocardiography allows physicians to take a disciplined, segmental approach to imaging the heart, he continued. After determining whether the heart is in the correct position, they can assess systemic venous drainage, pulmonary venous drainage, atrioventricular connections, ventriculoarterial connections, and intra- and extracardiac structures.

Ultrasound is useful for assessing virtually every type of congenital heart defect, including ventricular septal defects, the most common form of CHD, according to Dr. Friedman. Physicians can confirm the clinical diagnosis and see the defect's location in the ventricular septum. They can measure size, flow, and pressure across

the defect. Small probes enable the use of transesophageal echocardiography (TEE) in children of all ages. Dr. Friedman said TEE provides excellent anatomic definition because lungs, bone, and muscle do not interfere with the imaging.

“We are looking right at the back of the heart from the esophagus. There is nothing in between,” he said.

Dr. Friedman recommended TEE for assessing very small, hard-to-see abnormalities. “If endocarditis is suspected, trans-

esophageal electrocardiogram might be the way to go.”

It is also useful, he added, for the Fontan patient and others who require surgery. Whereas thoracic echo is not practical in the operating room, he said a probe in the esophagus can provide information during surgery and assess the adequacy of repair for better postoperative management.

TEE is also useful in the cath lab, he continued. It helps define pathophysiology and is an alternative to imaging methods

that expose the patient to radiation.

With three-dimensional echocardiography, he said, physicians can obtain beautiful, real-time pictures of the atrial septum, mitral valve, and aortic valve structure.

Three advances—radionuclide imaging, positron emission tomography, and computed tomography—are increasingly used, but Dr. Friedman urged caution because they expose children to ionizing radiation.

Radionuclide imaging allows accurate

Continued on following page

IN PAH, TAKE AIM AT ET-1 THROUGH ET_A SELECTIVITY

Circulating levels of ET-1, the most potent subtype of ET, have been associated with disease severity in PAH.¹ The deleterious effects of elevated ET-1 include cellular proliferation, vasoconstriction, and vascular remodeling.²⁻⁴

In pulmonary arterial hypertension (PAH), endothelin (ET-1) exerts its cardiovascular effects through 2 receptors: ET_A and ET_B. When ET-1 activates the ET_A receptor on the vascular smooth muscle, it leads to vasoconstriction and vascular remodeling.^{4,5} Endothelial ET_B receptors mediate the release of vasodilating nitric oxide (NO) and prostacyclin (PGI₂), while inhibiting and clearing ET-1 from circulation.^{5,6} Blockade of ET_B receptors may significantly impair the balance of endothelium-derived vasodilating substances.^{4,7}

Endothelial dysfunction has been shown to improve with selective ET_A blockade.⁸ Hence, preemptive targeting of ET-1 through selective ET_A receptor antagonism can slow the progression of PAH, and may even provide better overall outcomes.^{2,4,8}

TARGETED ET-1 TREATMENTS MAY PROVIDE BETTER OUTCOMES

Imbalances in the key endothelial cell-derived mediators NO, PGI₂, and specifically ET-1 are thought to be central to the pathogenesis of PAH.⁹ NO and PGI₂ are potent vasodilators with antiproliferative activity.¹⁰ ET-1 is a potent vasoconstrictor with proliferative activity.⁵ Chronically elevated levels of ET-1 are associated with pulmonary vascular resistance, excessive scar formation and cardiac remodeling, cellular proliferation, and cardiac hypertrophy.^{1,11-13}

A reduction of excess ET-1 levels may result in positive outcomes for patients with PAH. It has been shown that in patients with congestive heart failure, elevated ET-1 plasma

Figure 1: ET_A receptor pathway

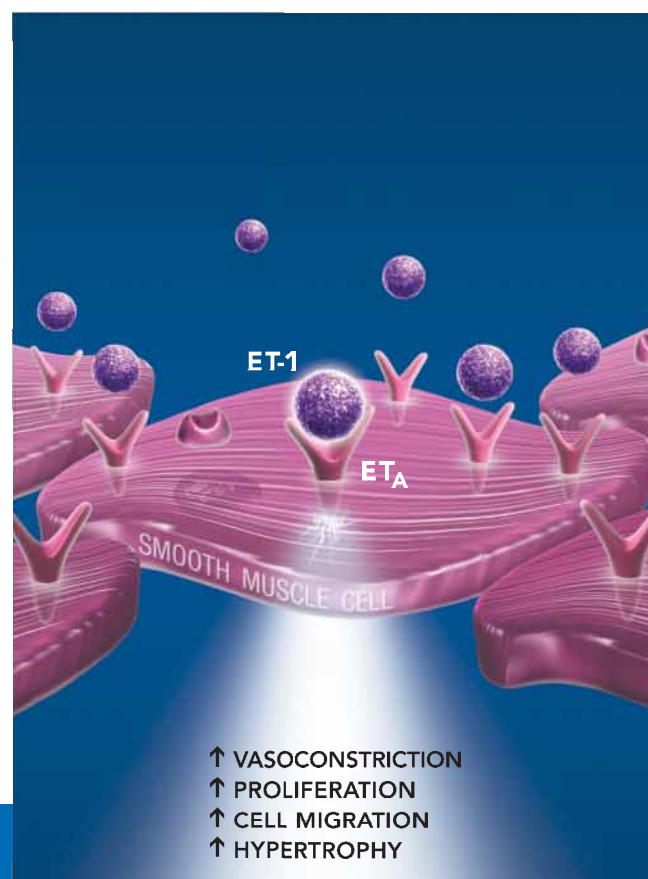
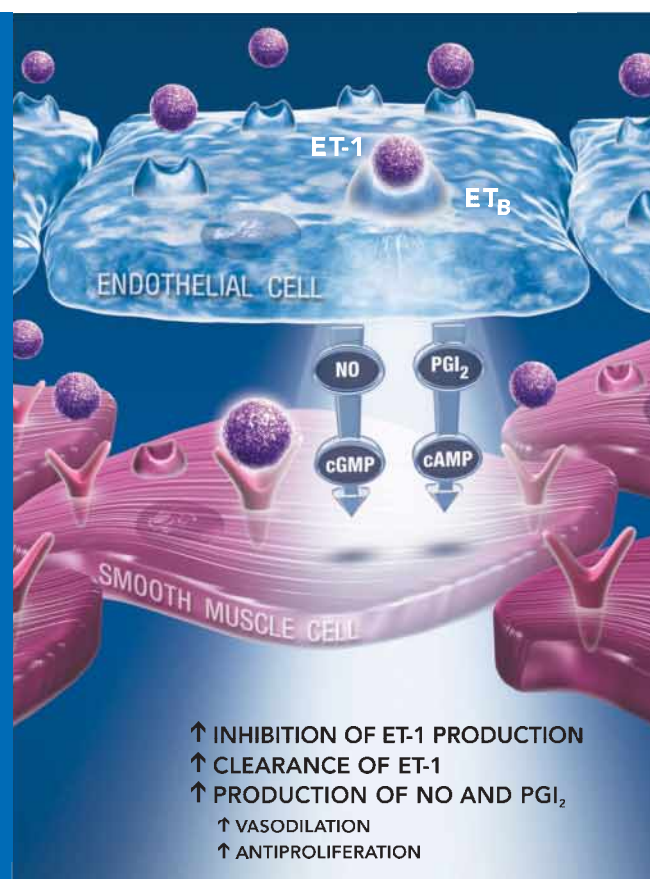
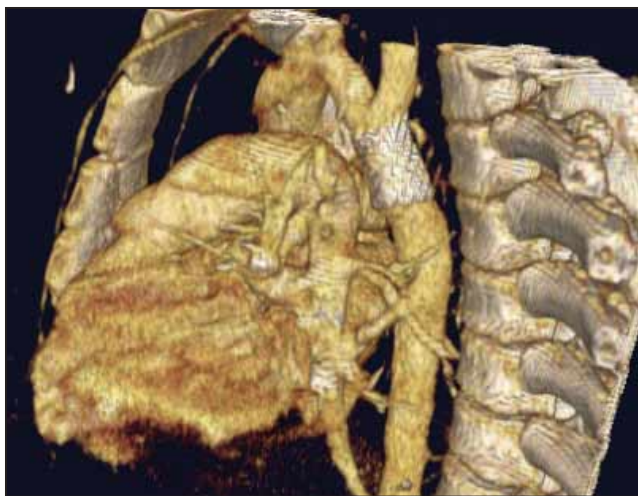
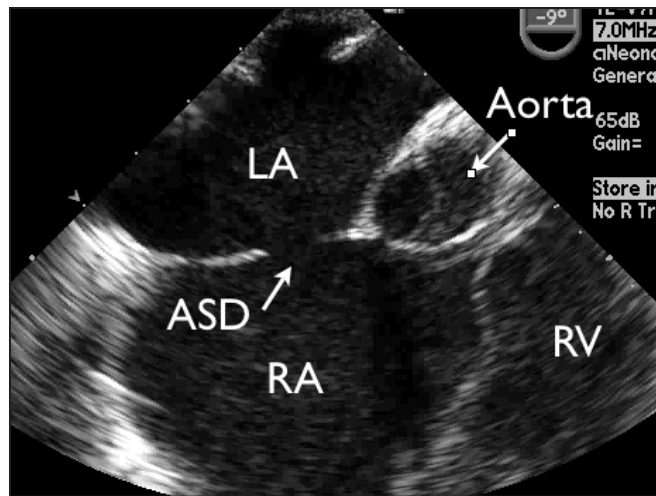


Figure 2: ET_B receptor pathway





A CT scan with three-dimensional reconstruction shows a stent placed in this patient to aortic coarctation. With three-dimensional echocardiography, physicians can obtain real-time images of the atrial septum, mitral valve, and aortic valve structure.



A transesophageal echocardiogram shows a secundum atrial septal defect (ASD) in a toddler. This technology provides excellent anatomic definition because lungs, bone, and muscle do not interfere with the imaging (LA, left atrium; RA, right atrium; RV, right ventricle).

PHOTOS COURTESY DR. ALAN FRIEDMAN

Continued from previous page

measurement of right and left ventricular function. Unlike echocardiography, its results are not subject to variable interobserver interpretation. He recommended PET scanning for assessing myocardial metabolism, perfusion, and viability.

Dr. Friedman said ultrafast CT scanning produces very-high-resolution images that can provide excellent information on blood flow and cardiac function. It also can assess areas of stenosis, particularly in the distal pulmonary artery, that are missed by echocardiography.

Although not yet portable, MRI and MR angiography also offer excellent resolution, according to Dr. Friedman, but without the high doses of radiation with CT scanning. Three-dimensional images are already available for surgical planning, he said, and MR cardiac catheterization laboratories are being developed. ■

Doppler Able to Determine the Nature of HCM

Doppler myocardial imaging to assess systolic activation delay can help determine whether a condition is hypertrophic cardiomyopathy or merely the result of athletic training—and help predict serious adverse cardiac events, Italian researchers reported.

Dr. Antonello D'Andrea of the Second University of Naples (Italy) and colleagues followed 70 patients with hypertrophic cardiomyopathy (HCM) and 85 age- and sex-matched competitive athletes with enlarged left ventricles and interventricular septa thicker than 12 mm (*Br. J. Sports Med.* 2006;40:244-50).

During the 4-year follow-up, the study's primary end point was cardiovascular mortality. Eight HCM patients died during follow-up; none of the athletes had a cardiovascular event. The participants were aged 29 years on average and were matched for blood pressure. Eighty percent of them were male. All had standard pulsed Doppler echocardiography and pulsed Doppler myocardial imaging in six myocardial segments. HCM patients showed a "significant global Doppler interventricular delay," the authors said. One-fifth of the HCM patients had a relative who had died from an HCM-related cardiac event.

—John R. Bell

levels are at least partly associated with impaired ET_B receptor-mediated clearance.¹³ Furthermore, the long-term administration of a selective ET_B receptor antagonist was found to have unfavorable effects on vascular remodeling.⁴ This is in sharp contrast to the benefits of selective ET_A antagonism.¹⁴

THE DIFFERENCE LIES IN ET_A SELECTIVITY

Vasoconstriction, cellular proliferation, and vascular remodeling are the hallmarks of PAH.¹² Studies have demonstrated that selective ET_A antagonists play a pivotal role in the regulation of ET-1 levels in PAH and have been beneficial for vascular remodeling.^{4,7,13}

ET-1 AND RECEPTOR-MEDIATED ACTIVITIES

Highly selective ET_A blockade maintains ET-1 clearance, NO and PGI₂ levels, and reduces or maintains circulating ET-1 levels, resulting in vasodilation, increased blood flow, and repair of remodeled vasculature compared to less selective agents.^{5-7,14} (See Figures 1,2)

HOW SELECTIVE TO ET_A SHOULD TREATMENT BE?

The more selective, the better. One should always be aware of the varying degrees of selectivity, as they equate to differences in blockade of the ET_A and ET_B receptors and resulting levels of ET-1.^{8,15,16} Figure 3 illustrates the difference between a less selective agent and highly selective agents. These in vitro selectivity ratios demonstrate the stark differences in ET_A selectivity. Figure 4 depicts how agents with low selectivity of the ET_A receptor (<2400) increase ET-1 levels whereas highly selective ET_A receptor (>2400) antagonists have been shown to

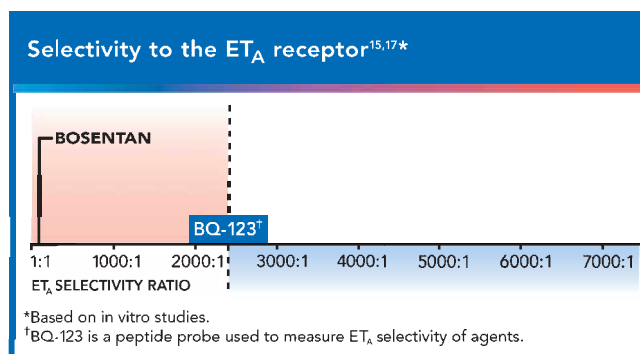


Figure 3

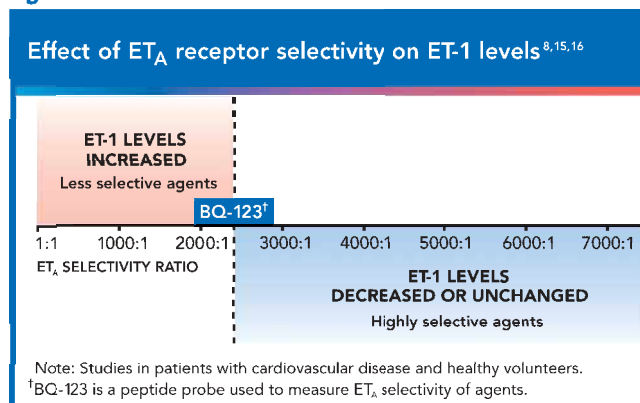


Figure 4

decrease ET-1 levels or leave them unchanged.^{6,8,15} The benefits of ET_A selectivity are being recognized.

TOWARD BETTER OUTCOMES IN PAH

Currently, there are no highly selective ET_A antagonists available for the treatment of PAH. In vivo studies have shown that highly selective ET_A antagonism may lead to better overall outcomes.^{7,8,12}

References: 1. Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. *Chest*. 2001;120:1562-1569. 2. Lüscher TF, Yang Z, Tschudi M, et al. Interaction between endothelin-1 and endothelin-derived relaxing factor in human arteries and veins. *Circ Res*. 1990;66:1088-1094. 3. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. 1988;332:411-415. 4. Murakoshi N, Miyauchi T, Kakinuma Y, et al. Vascular endothelin-B receptor system in vivo plays a favorable inhibitory role in vascular remodeling after injury revealed by endothelin-B receptor-knockout mice. *Circulation*. 2002;106:1991-1998. 5. Peacock AJ, Rubin LJ, eds. *Pulmonary Circulation: Diseases and Their Treatment*. 2nd ed. London: Arnold; 2004. 6. Fukuroda T, Fujikawa T, Ozaki S, Ishikawa K, Yano M, Nishikibe M. Clearance of circulating endothelin-1 by ET_B receptors in rats. *Biochem Biophys Res Commun*. 1994;199:1461-1465. 7. Verhaar MC, Strachan FE, Newby DE, et al. Endothelin-A receptor antagonist-mediated vasodilatation is attenuated by inhibition of nitric oxide synthesis and by endothelin-B receptor blockade. *Circulation*. 1998;97:752-756. 8. Halcox JPJ, Nour KRA, Zalos G, Quyyumi AA. Coronary vasodilation and improvement in endothelial dysfunction with endothelin ET_A receptor blockade. *Circ Res*. 2001;89:969-976. 9. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993;328:1732-1739. 10. Hankins SR, Horn EM. Current management of patients with pulmonary hypertension and right ventricular insufficiency. *Curr Cardiol Rep*. 2000;2:244-251. 11. Spieker LE, Noll G, Ruschitzka FT, Lüscher TF. Endothelin receptor antagonists in congestive heart failure: a new therapeutic principle for the future? *J Am Coll Cardiol*. 2001;37:1493-1505. 12. Jeffery TK, Wanstall JC. Pulmonary vascular remodeling: a target for therapeutic intervention in pulmonary hypertension. *Pharmacol Ther*. 2001;92:1-20. 13. Lüscher TF, Barton M. Endothelins and endothelin receptor antagonists: therapeutic considerations for a novel class of cardiovascular drugs. *Circulation*. 2000;102:2434-2440. 14. Chen SJ, Chen YF, Oppenorth TJ, et al. The orally active nonpeptide endothelin A-receptor antagonist A-127722 prevents and reverses hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling in Sprague-Dawley rats. *J Cardiovasc Pharmacol*. 1997;29:713-725. 15. Ihara M, Noguchi K, Saeki T, et al. Biological profiles of highly potent novel endothelin antagonists selective for the ET_A receptor. *Life Sci*. 1992;50:247-255. 16. Williamson DJ, Wallman LL, Jones R, et al. Hemodynamic effects of bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. *Circulation*. 2000;102:411-418. 17. Clozel M, Breu V, Gray GA, et al. Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist. *J Pharmacol Exp Ther*. 1994;270:228-235.