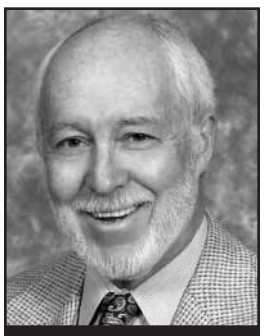
IN PERSPECTIVE

At Last, an Antioxidant Triumph

The results of the African American Heart Failure Trial surprised many people and sparked debate about race-based differences in clinical outcomes and even whether race should be a focus of clinical studies.



BY JONATHAN ABRAMS, M.D.

In A-HeFT, 1,050 self-identified African American patients with heart failure were given BiDil—a combination of 20 mg of isosorbide dinitrate (ISDN) and 37.5 mg of hydralazine—or a placebo three times daily. The regimen significantly decreased mortality (risk reduction 43%), improved quality of life, and reduced first hospital admissions for heart failure (risk reduction 33%). The study was stopped prematurely, after a mean of only 10 months.

This drug combination has a long history and was used in the Veterans Affairs Vasodilator-Heart Failure Trial I and II (V-HeFT I and II) in the 1980s. But BiDil has never achieved widespread use in the treatment of heart failure.

Why then should this study, and the Food and Drug Administration's approval of BiDil for treating African American heart failure patients this June, be of particular interest? The answer may relate to possible differences in vascular biology between blacks and whites, with some studies suggesting a lesser vasodilator response to endothelial-dependent stimuli in healthy blacks during endothelial function testing, that is, less nitric oxide availability to the vessel wall.

Another arcane fact appears to have played a pivotal role. Hydralazine, a well-known but little-used potent vasodilator and antihypertensive agent, is a free radical scavenger, or antioxidant. Jay N. Cohn, M.D., the progenitor of V-HeFT I and II, recognized that hydralazine might play an unusual role when used with ISDN: The antioxidant actions of hydralazine would decrease ISDN-induced oxidative stress, allowing for full expression of nitrate vasodilator effects.

Such a rationale derives from recent work indicating that nitrates rapidly induce oxidative stress in the blood vessel wall, a phenomenon that appears to be related to the development of nitrate tolerance. Several intracellular actions result in decreased availability and functionality of nitric oxide. Nitrate exposure results in peroxynitrite production, as well as substantial impairment of the arginine–nitric oxide axis. Hydralazine might reverse or prevent degradation of endothelial nitric oxide synthase function and decrease nitric oxide production, resulting in enhanced nitrate vasodilator capacity. Thus, this drug combination may prevent nitrate tolerance, a prooxidative stress state.

These explanations are only hypotheses. One can track this story back to trials on acute myocardial infarction in the mid-1990s, such as the Italian Study Group for Streptokinase in Myocardial Infarction (GISSI-3) and the Fourth International Study of Infarct Survival (ISIS-4), to speculate that the relative ineffectiveness of nitrates in these huge randomized clinical trials may have been due in part to the induction of partial nitrate tolerance with resultant oxidative stress, occurring well off the radar screen. Curiosity and persistence to investigate this hypothesis seem to have paid off. Perhaps, at last, we have an antioxidant compound that will truly provide benefit to our patients. ■

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Percutaneous VADs Provide Short-Term Help in Heart Failure, Surgery

BY JEFF EVANS
Senior Writer

WASHINGTON — Short-term use of a percutaneous ventricular assist device during high-risk surgery or in cases of near-death heart failure can help support patients long enough for them to recover or receive additional treatment, Reynolds M. Delgado III, M.D., said at the annual conference of the American Society for Artificial Internal Organs.

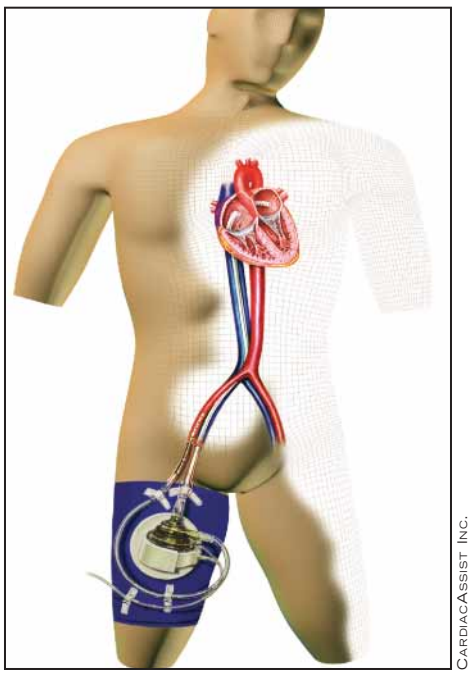
Dr. Delgado and his colleagues at the Texas Heart Institute have used the TandemHeart in four different scenarios as:

- A supportive device during high-risk percutaneous transluminal coronary angioplasty in nine patients.
- A bridge to recovery in two patients with acute cardiogenic shock.
- Circulatory support in five patients during high-risk cardiac surgery (coronary artery bypass and/or mitral valve surgery).
- A bridge to an implanted left ventricular assist device (LVAD) in seven patients.

Blood flow in the TandemHeart, made by CardiacAssist Inc., follows a path from a cannula in the femoral vein that pierces the intraatrial septum and takes oxygenated blood from the left atrium back to a continuously flowing extracorporeal pump (attached to the patient's leg), which distributes the blood through a cannula in one or both femoral arteries.

"The tricky part of this procedure is the transseptal cannulation; putting this venous catheter across the septum requires some special skill. A subset of cardiologists are able to do this—perhaps 10% or less," said Dr. Delgado, medical director of mechanical assist devices in heart failure at the institute, located at St. Luke's Episcopal Hospital, Houston.

None of the high-risk percutaneous transluminal coronary angioplasty patients were candidates for surgery. They had high-risk coronary anatomy and were at risk for imminent death without intervention. The investigators successfully performed the procedure without complications in eight of these nine patients; one patient had a perforated left atrium. Overall, eight patients were discharged from the hospital with good long-term outcomes while one patient died of multiorgan failure after surgery, said Dr. Delgado, a cardiologist. Dr. Delgado reported that he was an investigator on a previous trial sponsored by CardiacAssist but has no financial conflicts of interest with the company.



CARDIACASSIST INC.

A pump circulates blood via a cannula that pierces the intraatrial septum.

Both cardiogenic shock patients successfully underwent the implantation procedure. After 7 days, one patient successfully recovered from heart failure due to acute myocarditis. The other patient initially suffered an acute MI and then cardiac arrest just prior to implantation of the TandemHeart; the patient died despite successful implantation.

Of five patients who underwent high-risk cardiac surgery, all had successful implantation, but one patient with coagulopathy and multiorgan failure died of major intraoperative bleeding.

Seven patients were successfully bridged from the TandemHeart to an LVAD. However, four of these patients did not survive long term with an LVAD, primarily because of multiorgan failure that existed prior to the implantation of the TandemHeart.

On average, the 23 patients in the study were aged 68 years and were on percutaneous ventricular assist device support for 2.8 days; 20 patients were male. ■

Preventing Right Heart Failure in LVAD Patients

WASHINGTON — Measuring markers of inflammation and neurohumoral activation in candidates for implantation with a left ventricular assist device may help predict the probability of right ventricular failure, Evgenij V. Potapov, M.D., reported at the annual conference of the American Society for Artificial Internal Organs.

"The problem is that up to 20% of patients receiving a left ventricular assist device [LVAD] develop right heart failure," Dr. Potapov, a cardiothoracic surgeon at the Deutsches Herzzentrum Berlin, said in an interview.

Dr. Potapov and his colleagues reviewed the records of patients with chronic end-stage heart failure who received an LVAD during 2002-2004.

They found no differences in preoperative echocardiographic findings or laboratory or hemodynamic parameters between the 102 patients who had normal right ventricular function after LVAD implantation and the 9 patients with right ventricular failure, defined as having at least two of the following within 24 hours of LVAD implantation: mean arterial pressure less than 55 mm Hg, central venous pressure less than 16 mm Hg, mixed venous oxygen saturation less than 55%, cardiac index less than 2 L/min per square meter, and more than 20 inotropic equivalents of inotropic support.

But a subsequent prospective study of 40 patients found that people with normal right ventricular function after left ventricular assist device implantation had significantly lower levels of markers of inflammation (procalcitonin and neopterin) and neurohumoral activation (N-terminal pro-B-type natriuretic peptide and big endothelin-1) than did those who would later develop right ventricular failure, he said in a poster session at the conference.

Patients who are identified as having a high probability of right ventricular failure after implantation of a left ventricular assist device could instead undergo implantation of a biventricular support device or a total artificial heart, Dr. Potapov suggested.

None of the patients who were in either study required a left ventricular assist device for postcardiotomy heart failure.

—Jeff Evans