'Wall Motion Delay' Could Predict Success of CRT

BY BRUCE JANCIN
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VANCOUVER, B.C. — Baseline echocardiographic evidence of mechanical ventricular dyssynchrony is a powerful predictor of the long-term clinical benefit of cardiac resynchronization therapy in patients with severe heart failure, Maria Vittoria Pitzalis, M.D., said at a meeting sponsored by the International Academy of Cardiology.

Indeed, echocardiographic ventricular dyssynchrony is such a strong predictor that it ought to replace ECG evidence of prolonged QRS duration as a major screening criterion for cardiac resynchronization therapy (CRT) patient eligibility, added Dr. Pitzalis, who did her groundbreaking work in this field while at the University of Bari (Italy).

'If a [wall motion] delay doesn't exist at baseline, you're not improving anything' with CRT.

DR. PITZALIS

In the past few years, CRT has emerged as a major therapeutic advance for patients with severe heart failure despite optimal medical management. Studies have shown CRT results in reverse left ventricular remodeling as reflected in increased left ventricular ejection fraction, improved exercise tolerance and New York Heart Association functional class, enhanced quality of life, fewer hospitalizations, and, most recently, in the Cardiac Resynchronization in Heart Failure (CARE-HF) trial, a 36% reduction in all-cause mortality.

However, about one-quarter of treated patients do not benefit from CRT. There is great interest in developing ways to identify them in advance so as to spare them the expense of the device therapy as well as the risks associated with the at-times technically challenging transvenous lead placement.

A prolonged QRS interval has been a requirement for participation in all of the major CRT trials and is routinely used as a screening criterion for CRT eligibility in clinical practice. A long QRS is an ECG marker for ventricular dyssynchrony. But there is increasing dissatisfaction with its use as a screening tool in light of clear evidence that some patients with a normal QRS duration have echocardiographic evidence of mechanical ventricular dyssynchrony while others with a long QRS do not.

Dr. Pitzalis and her Italian coworkers have developed an echocardiographic method of assessing patients for ventricular dyssynchrony using a standard two-dimensional Doppler short-axis view at the papillary muscle level. It is obtained by calculating the shortest interval between the greatest posterior displacement of the septum and the maximum displacement of the left posterior ventricular wall. They call it the septal-to-posterior wall motion delay (SPWMD). It's simple, reproducible, widely available, and doesn't require specialized techniques and equipment, unlike tissue Doppler imaging, an alternative echocardiographic means of assessment for ventricular dyssynchrony.

The cardiologist presented a prospective study involving 60 patients, with severe heart failure and left bundle branch block, who underwent CRT. All had a baseline QRS greater than 130 milliseconds, and all underwent baseline measurement of SPWMD.

During a median 14-month follow-up, 4 patients died of heart failure and 12 others were hospitalized for worsening heart failure. In a multivariate analysis, only baseline SPWMD was significantly associated with subsequent heart failure progression or improvement. A long septal-to-posterior wall motion delay—that is, at least 130 milliseconds—was present in 79% of patients who experienced clinical improvement as defined by an increase in left ventricular ejection fraction along with at least a one-class improvement in New York Heart Association functional class. Only 9% of patients with an SPWMD of less than 130 milliseconds experienced such improvement. Change in QRS duration in response to therapy was unrelated to these outcomes.

"If you think about this result, it's not illogical, because in those patients with a long baseline delay, you're correcting the delay with CRT and therefore you are modifying prognosis. If a delay doesn't exist at baseline, you're not improving anything," she said.

The investigators also compared the SPWMD results with those of tissue Doppler imaging and found no significant difference between the two echocardiographic techniques in terms of the end point of improved ejection fraction at 6 months.

Audience members inquired how they should manage patients who meet the now-standard prolonged QRS criterion for CRT implantation but have a short SPWMD.

"You can find very different things at the echocardiographic and ECG levels. There is dissociation between the two," Dr. Pitzalis said. "In my opinion, based on our results, if you don't have any ventricular mechanical dyssynchrony, the possibility that your patient will improve with CRT is very low—just 9%. I'm wondering if the QRS duration criterion could be eliminated in the next few years, because we know there are patients with a narrow QRS that have mechanical dyssynchrony, and if an echo evaluation shows a rather large dyssynchrony, we have to implant them with CRT because they will benefit in clinical and functional terms." ■

Heart Failure Drug Pipeline Full of Promising Newcomers

BY BRUCE JANCIN
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VANCOUVER, B.C. — The recent big therapeutic successes in heart failure have come from implantable electrophysiologic devices—cardiac resynchronization therapy, implantable cardioverter defibrillators—and surgical advances, such as ventricular reduction procedures.

Although attempts to develop new drugs have proved largely disappointing of late, that may be about to change, Robert E. Hobbs, M.D., said at a meeting sponsored by the International Academy of Cardiology.

Many heart failure drugs are working their way through the developmental process. Dr. Hobbs chose to highlight half a dozen, each having a different and novel mechanism of action.

Each of these drugs has shown promise in clinical trials, and each addresses a different hypothesis about the nature of worsening heart failure. And these six interesting drugs constitute only a portion of what's in the pipeline, added Dr. Hobbs of the Cleveland Clinic Foundation.

► **A xanthine oxidase inhibitor.** Oxypurinol, an analogue of allopurinol, inhibits xanthine oxidase, the enzyme that produces uric acid, as well as harmful oxygen free radicals. Xanthine oxidase is upregulated in heart failure. By inhibiting this enzyme, oxypurinol has been shown to improve myocardial energetics and endothelial function.

The Oxypurinol Therapy for Congestive Heart Failure (OPT-CHF) trial is a recently completed 400-patient phase II/III randomized double-blind trial. The data are now being analyzed and are due to be presented this fall at the annual meeting of the American Heart Association.

► **A unique inotropic agent.** Levosimendan's mechanism of action differs from that of other inotropes, such as dobutamine and milrinone. It binds to cardiac troponin C. Levosimendan is categorized as a calcium-sensitizing agent because it enhances myocardial contractility without increasing intracellular calcium concentrations. The drug also acts as a vasodilator through activation of potassium channels. Moreover, it's a weak phosphodiesterase inhibitor as well.

Levosimendan's hemodynamic effects include an increase in cardiac index along with systemic and coronary vasodilation. In heart failure patients, levosimendan reduces elevated intracardiac pressures without increasing myocardial oxygen consumption. Unlike other inotropes, it has low arrhythmic potential, Dr. Hobbs stressed. The drug is approved for use in more than 30 countries as a treatment for patients with decompensated heart failure in need of inotropic support. But not in the United States.

"In the United States, they're reinventing the wheel and taking the drug through repeats of the clinical trials," the cardiologist said. "I can't believe I'm still talking about levosimendan 10 years later. I was involved in clinical trials of the oral formulation a decade ago."

What's under study today, however, is the intravenous version of levosimendan. The 800-patient phase-III Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial is due to be presented in November at the AHA meeting.

► **A thyroid hormone analogue.** Roughly 30% of patients with advanced heart failure have low T_3 and normal TSH. Giving T_3 to patients with heart failure confers multiple cardiovascular benefits, including positive inotropic effects, improved diastolic relaxation, and stimulation of alpha-myosin heavy chain gene expression. But it also causes tachycardia, largely negating the improved cardiac performance.

Treatment with 3,5-diiodothyropropionic acid (DITPA), a T_3 analogue, offers similar cardiovascular benefits—but without the tachycardia. A 40-center, 34-week randomized trial is underway in 150 patients with class III/IV heart failure, low ejection fraction, low T_3, and normal TSH. Participants are assigned to one of two doses of DITPA or placebo.

► **An atrial natriuretic peptide.** Carperitide, a synthetic atrial natriuretic peptide, is an intravenous vasodilator approved for use in acutely decompensated heart failure in Japan for a decade. Its multiple effects are similar to those of nesiritide (Natrecor), recombinant brain natriuretic peptide.

An ongoing U.S. clinical trial is aimed at determining the safety and efficacy of seven different doses of carperitide in 158 patients.

► **Adenosine receptor antagonists.** These agents cause afferent arteriolar dilatation. They promote diuresis while preserving renal function and maintaining glomerular filtration rate. One agent—known at this point only as KW-3902—is the subject of an ongoing clinical trial in 200 hospitalized heart failure patients with impaired renal function. It's a 4-day treatment study with 30-day follow-up. "These agents look promising, but it's early," Dr. Hobbs commented.

► **Vasopressin antagonists.** Nicknamed "super diuretics," these drugs cause profound diuresis without disrupting electrolytes. The target of these drugs—vasopressin—is synthesized by the hypothalamus in response to baroreceptor and osmotic stimuli. It causes vasoconstriction and sodium and water retention.

Two vasopressin antagonists, or "vaptans," have been tested in clinical trials: conivaptan and tolvaptan. Ongoing is the large multinational phase III Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST). Results are probably several years off, according to Dr. Hobbs.

Udho Thadani, M.D., commented that heart failure patients already have a rather full plate just with today's standard medications, which include a β-blocker, an ACE inhibitor or angiotensin receptor blocker, an aldosterone blocker such as spironolactone, and digoxin.

If even a few of the drugs with novel mechanisms of action that are in the developmental pipeline eventually find their way into routine clinical practice on top of today's standard therapy, compliance issues will become a much more prominent concern, predicted Dr. Thadani, professor emeritus of medicine at the University of Oklahoma, Oklahoma City. ■