‘Wall Motion Delay’ Could Predict Success of CRT

BY BRUCE JANCIN  Denver Bureau

VANCOUVER, B.C. — Baseline echocardiographic evidence of mechanical ventricular dysynchrony 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 dysynchrony 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). But patient eligibility, added Dr. Pitzalis, who did her groundbreaking work in this field while at the University of Bari (Italy).

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 that a delay 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.

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 clinical practice, she said. Some patients with a normal QRS duration have echocardiographic evidence of mechanical ventricular dysynchrony while others with 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 mitral leaflet and the maximum displacement of the left posterior ventricular wall. They call it the septo-posterior wall motion delay (SP-WMD). It’s simple, reproducible, widely available, and doesn’t require specialized equipment or ultrasound expertise.

If a (wall motion) delay doesn’t exist at baseline, you’re not going to improve anything with CRT.

Dr. Pitzalis

There is dissociation between the two,” Dr. Pitzalis said. “In my opinion, based on our results, if you don’t have any ventricular mechanical dysynchrony, the possibility that your patient will improve with CRT is very low—just 9%.”

“I’m wondering if the QRS duration criteria will be eliminated in the next few years, because we know there are patients with a narrow QRS that have mechanical dysynchrony, and if you entrain them you have to get into them with CRT because they will benefit in clinical and functional terms.”

During a median 14-month follow-up, 4 patients died of heart failure and 12 others were hospitalized for worsening heart failure alone, Dr. Pitzalis said. Only baseline SP-WMD was significantly associated with subsequent heart failure progression or improvement. A long septo-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 a significant New York Heart Association functional class. Only 9% of patients with an SP-WMD 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 SP-WMD 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 SP-WMD.

“You will 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 dysynchrony, the possibility that your patient will improve with CRT is very low—just 9%.”

“I’m wondering if the QRS duration criteria will be eliminated in the near future, because we know there are patients with a narrow QRS that have mechanical dysynchrony, and if you entrain them you have to get into them with CRT because they will benefit in clinical and functional terms.”

Heart Failure Drug Pipeline Full of Promising Newcomers

BY BRUCE JANCIN  Denver Bureau

VANCOUVER, B.C. — The recent big therapeutic successes in heart failure have come from implantable electrophysiologic devices that are programmed to resynchronize implantable cardioverter defibrillators—and surgical advances, such as ventricular resection procedures.

Although attempts to develop new drugs have proved largely disappointing in late-stage clinical trials, they have demonstrated that there is great interest in developing therapies as well as the risks associated with them.

Many heart failure drugs are working their way through the developmental process. Dr. Hobbs chose to present these results with that of his long-acting form of levosimendan 10 years later. I was involved in clinical trials of the oral formulation a decade ago,” Dr. Hobbs said. “I can’t believe I’m still talking about levosimendan’s mechanism of action differs from that of other inotropic agents, such as dobutamine and milrinone. It binds to cardiac tropomyosin C. Levosimendan is categorized as a calcium-sensitizing agent because it enhances myocardial contractility without increasing intracellular calcium concentrations. The drug can also act as a vasodilator through activation of potassium channels. Moreover, it’s a weak phosphodiesterase inhibitor as well.

Levosimand’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 arrhythmogenic potential, Dr. Hobbs stressed. The drug is approved for use in more than 50 countries as a treatment for patients with decompen-

sated 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 repeated of the Heart Failure Trials,” Dr. Hobbs said. “I can’t believe I’m still talking about levosimendan 10 years later. I was involved in clinical trials of the drug at the American Heart Association meeting.

What’s under study today, however, is the intravenous version of levosimendan. The 800-patient phase-III Randomized Multi-center Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial is due to be presented next year at the annual meeting of the American Heart Association.

A thyroid hormone analogue. Roughly 30% of patients with advanced heart failure have low T3 and normal TSH. Giving T3 to patients with low T3 but normal TSH results in cardiovascular benefits, including positive inotropic effects, improved diastolic relaxation, and stimulation of alpha-myosin heavy chain troponin expression. But it also causes tachycardia, largely negating the improved cardiac performance.

Treatment with 3,5-diiodothyropropionic acid (DITPA), a T3 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 T3 and normal TSH. Participants are assigned to one of two doses of DITPA or placebo.

An atral 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), a 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 118 patients.

Adenosine receptor agonists. 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—vaso-

pressin—is synthesized by the hypothalamus in response to baroreceptor and osmotic stimuli. It causes vasocostriction and sodium and water retention.

Two vasopressin antagonists, or “vap-
tans,” have been tested in clinical trials: conivaptan and tolvaptan. Ongoing is the large multinational Natriuretic peptide 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 come through the developmental pipeline eventually find their way into routine clinical practice on top of today’s standard therapy, compliance issues may become a major con-

cern, predicted Dr. Thadani, professor emeritus of medicine at the University of Oklahoma, Oklahoma City.