Cardiac resynchronization therapy in the elderly heart failure patient

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Ms. BP is an 83 year old white female with a long history of congestive heart failure (HF). She is now symptomatic with minimal exertion, has a left ventricular ejection fraction (LVEF) of 20%. Her CHF is due to hypertension (HTN) plus coronary artery disease (CAD) and she is on angiotensin converting enzyme inhibitor (ACEI), furosemide, digoxin, spironolactone, low dose beta blocker and nitrates. Her beta-natriuretic peptide (BNP) in clinic is 3030 pg/ml, heart rate (HR) 100, blood pressure (BP) 89/43. She has rales, jugular venous distention and pedal edema. An II/VI pansystolic murmur is appreciated over her entire precordium and an S3 is apparent. Her electrocardiogram (ECG) is shown in Figure 1 and reveals sinus tachycardia with a prolonged QRS duration of 159 milliseconds. Her husband brings in a new article about Biventricular pacing and asks you if it will help her.

You review her most recent echocardiogram which reveals: LV chamber severely enlarged (LV end diastolic dimension=6.2 cm); Wall motion globally impaired (LVEF=20%); Right ventricle (RV) at normal size with moderate to severe RV dysfunction; Left atrium (LA) moderately to severely enlarged; Right atrium (RA) mildly to moderately enlarged; Moderate to severe mitral regurgitation; Severe tricuspid regurgitation (TR); Estimated cardiac output=3 L/min; Pulmonary artery systolic pressure 89 mmHg; And impaired LV relaxation. Her husband is very socially conscious and you anticipate a bevvy of questions. What is your response?

Fig.1. The patient’s ECG reveals sinus tachycardia with a prolonged QRS duration of 159 milliseconds

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Biventricular pacing or cardiac resynchronization therapy (CRT) is a relatively new intervention for patients with dilated hearts resulting in heart failure. Since its initial application to patients, it has experienced a growth from limited applicability to increasingly wide usage. The published experience with CRT involved thousands of patients. Conceptually, one can imagine a large left ventricle that is activated in an uncoordinated fashion so that blood just sloshes around the ventricle instead of being ejected as in a well timed homogeneously activated ventricle (see figure 2). This lack of coordination is termed dyssynchrony.

Operationally, the pacing electrodes are placed in the RV apex and in the coronary sinus (CS) and the delay between impulses is manipulated so that the ventricle is activated and contracts in a more coordinated fashion (Figure 3). The CS electrode serves to activate the lateral or free wall of the LV.

Patients, whom others have suggested would benefit from CRT: those with functional New York Heart Association class III or IV HF, that is, who are symptomatic at rest or with minimal exertion; a wide QRS complex on ECG (duration of at least 130 or sometimes > 150 milliseconds), reduced LVEF (≤ 35%), enlarged LV cavity (end diastolic diameter of > 55 mm), and on optimal medical therapy. Because the intervention is expensive and potentially dangerous, the patients really must be on maximum medical therapy, and should not “past the point of no return”.

The studies of CRT have shown clear benefits, including arrhythmia prevention, increased survival, reduced hospitalizations from worsening CHF, improved systolic function at lower energy cost, increased exercise performance, and improved quality of life (QOL). The subjective improvements in QOL may be greater than any of the objective, functional parameters. For example, in the MIRACLE study, six minute walk distances increased 30 meters at one month after CRT placement and 40 meters at six months from baseline. These benefits while modest are not trivial when considering that many of the patients had end-stage heart failure. QOL scores in these patients improved significantly after CRT. In particular, some patients with significant mitral regurgitation had their regurgitant fraction decreased remarkably by CRT. Approximately one-third of patients did not respond symptomatically to CRT, and approximately one third did not improve their ejection fractions. Surprisingly there was no consistent overlap between the two groups.

Early reports of CRT’s effects seemed to be limited to short term symptomatic and functional improvement, but in more recent studies there appears to be a more profound, enduring effect. Specifically, in a subgroup of patients, CRT alters or reverses remodeling so that there is a decrease in left ventricular diameters and persistent improvement in systolic function. This moves CRT from a palliative procedure to one that alters the progression of the illness and may impact the decision-making process.

Survival is not a good measure of success for most of geriatric patients like MS BP. CHF is a horribly morbid disease in this population, and QOL or improved functional status is the key outcome. However, relatively few patients over the age of 75 and even fewer older women are included in these studies. As shown in Table X, it is likely that less than 200 women comparable to Ms. BP have been included in published studies.

Figure 4. Intraventricular delay as demonstrated by Yu et al with tissue Doppler imaging performed at different ventricular regions. At baseline, there was marked regional variation in Tₚ among the left ventricular segments and between the left and right ventricles. The Tₚ was earliest in the basal anteroseptal segment and latest in the basal lateral segment. After biventricular pacing therapy, the Tₚ was homogeneously delayed to a timing close to that of the basal lateral segment so that regional variation in Tₚ was abolished.
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CRT, just as more conventional pacing, allows upward titration of beta-blockers to optimal levels. The inability to reach therapeutic doses of beta-antagonists in the elderly with heart failure has been a frequent challenge in our experience. Having the safety net provided by CRT should allow one to fully attain recommended doses of beta-blockers and thus fully reap their benefits.

The presence of atrial fibrillation likely decreases the efficacy of CRT, but to a varying extent. While some have recommended atrioventricular node ablation at the time of CRT, this may not be absolutely necessary. Preliminary studies do show less improvement in QOL for those who remain in AF, but these need confirmation.

Placing the electrodes for CRT is technically challenging and complications do occur. Like all pacemakers, complications include pneumothorax, hemothorax, perforation, pocket hematoma, pocket infection, and lead infection. Biventricular pacers also can have significant difficulties in lead placement in at least 10% of patients, coronary sinus dissection or coronary perforation may occur in approximately 4%, extra cardiac stimulation of the diaphragm or phrenic nerves in at least 2%, perforations of the heart in 1%, and leads dislodging in 2-6%. The software is also sophisticated and generator dysfunction occurs in about 5% of patients. Finally unsuccessful procedures are seen in 8-12% though this number may be decreasing as experience increases, and acute heart failure decompensation may occur even after successful procedures. While data specific to CRT were not easily available, comparable data from dual lead DDD pacemaker placement suggest that these complications are serious when they occur. For example, in the MOST trial, two-thirds of all complications required reoperation, 85% of the patients with ventricular lead complications, and 94% of the patients with infection. The complications and their severity is just another factor in choosing which older patients should be considered for CRT.

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One approach that seems promising is to just place a single pacing lead in combination with the native activation. For example, preliminary studies suggest that a well placed left ventricular lead will provide the same acute changes in ejection fraction, mitral regurgitation, and ventricular dyssynchrony as biventricular pacing. The benefits of single left ventricular leads for CRT appear to persist over at least one year. Unfortunately, most of the technical challenges provided by CRT are those associated with the left ventricular (or coronary sinus) lead so the practical implications of this advance remain unclear. Additionally, perhaps by worsening dyssynchrony, a recent report suggests that single lead (primarily right ventricular) pacing may increase one’s probability of developing heart failure. Therefore the electrical and functional (rather than anatomic) locations of leads in the dyssynergic heart is critical.

Because of the sizable minority that does not get subjective benefits from CRT and its great expense (described below), choosing the best candidates has become a priority. Even with technically successful CRT, the number of non-responders is high. Estimates of 25-33% are frequent. Using tissue Doppler, investigators have looked for contractile dyssynchrony, rather than simply electrical heterogeneity reflected by the wide complex on ECG. The degree of intraventricular and interventricular asynchrony and their combination were the best predictive factors of LV functional recovery and reversed remodeling after cardiac resynchronization therapy in their hands. Others have found the technique useful, but less so than what reported by Penicka and colleagues and have utilized other measures (see below). The non-responders are becoming better characterized and the lack of dyssynchrony as well as the inability of the CRT to shorten the QRS duration on ECG are potent predictors of limited improvement with CRT placement. For example, in Lecoq’s experience with almost 150 patients, the non-responders (28% of the group) had less wide QRS complex (180 vs 192) and narrowing of only 11 ms of the QRS complex after CRT compared to narrowing of 37 ms in the responders.
This may mean that left ventricular electrode was in a suboptimal place in the left ventricle or that dyssnergy was not contributing to the ongoing heart failure in this subgroup of patients. Confirmation of the importance of having dyssnergy for the CRT to be of benefit comes from the recent work of Pitzalis. In patients where echocardiogram documented significant delay between septal contraction and posterior wall contraction, gains in cardiac function with CRT were seen in 80% of the cases. In patients without such delay, CRT only improved cardiac function in 9% of cases. That means over 90% without this measure of dyssnergy had CRT placed and did not benefit from this treatment. Further characterizations of the non-responders will provide mechanisms for continued improvements in targeting potential candidates.

Unfortunately the relationship between wide QRS and delay between septal and free wall contraction may be less strong than one would expect. Recently Bleeker and colleagues found 33% of those with heart failure, reduced ejection fractions and narrow QRS had significant dyssnergy and the potential to benefit from CRT. The assumption that ECG can act as a screening device for CRT may be incorrect.

As Ms. BP did, many older patients with CHF due to systolic dysfunction also have diastolic dysfunction. In fact, diastolic heterogeneity occurs as part of normal aging. Because CRT actually prolongs systole (Figure 6), delaying activation in many parts of the heart, it could decrease time available for left ventricular filling. However, by decreasing heterogeneity, CRT actually increases filling time in younger people which should help diastolic filling. In younger people with evidence of elevated LV filling pressure and a restrictive picture on mitral Doppler, CRT appears to actually improve diastolic filling and diastolic function. In those without an E/A ratio greater than 1, there was no improvement seen. Whether these findings will be confirmed in the elderly is an important yet unanswered question.

An informal survey was performed last year polling researchers who have published articles on CRT, and 10 responses were received. All respondents agreed that there was essentially nothing in the literature to guide decision-making for the patient over age 80, like Ms. BP. Participants also reported a significant selection bias toward “healthier” patients in this age group who underwent the CRT procedure. Some reviewed their experiences systematically and thought that there were no differences in efficacy between their younger and the selected older patients; others believed that the benefits of CRT would be decreased in their older patients. As to whether they believed there were increased complications in the elderly, the respondents were divided evenly into those that thought the rate of complications was comparable between old and young and those that had higher complications in the elderly. Many of the respondents suggested that financial and social issues were important considerations. Participants called for studies that were specific to the elderly.

Finally in the select group that CRT is indicated, should the patients get combined ICD and CRT therapy? Again the data are not clear cut, although studies showed equivalence or benefit for the combination. In the Minnesota experience, reviewed retrospectively, the mortality was tripled in the CRT alone (41%) compared to the CRT+ICD (13%) patients. As expected, relatively few were elderly or female in their population. In contrast, in large prospective studies, there was no difference in mortality between the groups. For example, CRT reduced the risk of death from any cause by 24 percent and CRT+ICD reduced the risk by 36 percent. Again, although survival is clearly not a trivial outcome, QOL and functional state are more important to elderly patients with limiting CHF. Whether the combination modifies these outcomes compared to CRT alone is uncertain.

In the United States, the cost for pacemakers ranges from $25,000 to $40,000; however, the total cost including hospital and professional fees may reach up to $100,000 in those with complicated courses. As congestive heart failure has mortality rates that outstrip colon cancer, discussions at a time of clinical stability should provide an end of life issues. Once patients are ill and unable to make their voices heard, families and physicians are reticent of to turn off pacemakers of all types, and death may be unnecessarily painful and uncomfortable in patients with CRT and ICD’s.

In conclusion, I do not think that the answer to Ms. BP and her husband should be an automatic yes, nor should it be an automatic no. I am not ready to say cardiac resynchronization therapy should be routinely offered to eligible patients experiencing heart failure. Instead CRT should be used in a small subset of older people. Which older patients are most likely to benefit is being slowly defined. Studies of this intervention should be conducted on older patients with low ejection fraction heart failure alone to examine efficacy and complication rate, rather than just adding a few non-representative elders to large studies focused on a younger age group. This will provide physicians evidence upon which to base decisions for patients like Ms. BP.

Reference


