Editorial

Cardiac Resynchronization Therapy Upgrade
Verschlimmbesserung?

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The implant rates of cardiac resynchronization therapy (CRT) increased rapidly through the first decade of this millennium but have plateaued more recently and may even have started to decrease in Europe and the United States.[1,2] The upgrade of existing pacemakers and implantable cardioverter defibrillators (ICDs) to CRT currently accounts for a quarter of all CRT procedures[3] and is a potential growth area. Kiehl et al[4] recently showed that 12.3% of patients with preserved left ventricular (LV) function who were implanted with a pacemaker for complete heart block developed pacing-induced cardiomyopathy, but the small proportion that underwent CRT upgrades responded well echocardiographically. The 2012 ACCF/AHA/HRS (American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society) Guideline[5] gives a class IIA recommendation to CRT upgrade at generator replacement if LV function is severely impaired and the expected pacing requirement is high. The 2013 ESC (European Society of Cardiology) guideline[6] goes further and gives a class I (level of evidence B) recommendation to CRT upgrade in device patients with LV ejection fraction <35% and high-percentage ventricular pacing. Advances in left ventricular lead design and lead delivery systems mean that CRT is usually technically straightforward and a much quicker procedure than ever before. Should we, therefore, be upgrading more patients with LV leads? The ACCF/AHA/HRS and ESC device upgrade guidelines are not based on any large randomized studies. Although data exist that heart failure patients with left bundle branch block and a QRS duration >150 ms are most likely to respond to de novo CRT therapy,[7] it is not clear whether upgrade patients respond in the same way.

See Article by Vamos et al

In this respect, Vamos et al[8] are to be congratulated for adding to the body of evidence about the benefit of cardiac resynchronization therapy defibrillators (CRT-D) in patients undergoing an upgrade procedure compared with a new implant. It is important to note that in this multicenter, prospective study, the de novo implant and upgrade populations had differences that could not be fully corrected for. Nonetheless, the data are interesting. The disparity in baseline characteristics between the 2 study groups perhaps reflects the fact that de novo and upgrade patients are different heart failure populations. In particular, the upgrade patients in this study were more likely to require a CRT-D for secondary prevention and had more comorbidities. Perhaps it is thus not surprising that upgrade patients had a worse symptomatic response and survival compared with the de novo implant patients. The upgrade patients in this study had a broader baseline QRS, but a significantly lower proportion of patients had a typical LBBB pattern. It is interesting to note, however, that even in those patients with a broad LBBB (QRS >150), the response rate in the upgrade group was (nonsignificantly) lower than in the de novo implant patients and not much higher than the overall response rate in the upgrade population. The suggestion is that even in upgrade patients who have similar electrical characteristics to de novo implant patients that respond to CRT, their comorbidities and electromechanical substrate may be such that they do not respond as well to therapy.

Verschlimmbesserung?

Verschlimmbesserung is a colloquial German term meaning making things worse in an attempt to make things better. The CRT response rate of 57% seen in the upgrade population in this study may seem similar to the response rate for de novo implants seen in other CRT studies but it must be noted that this was the symptomatic response rate. Analysis of the large randomized CRT studies has shown that up to 35% of control patients may see an improvement in their New York Heart Association class and that the absolute incremental improvement provided by CRT over control may be as low as 16%.[9] Interestingly, the mortality rate seen in the upgrade group in the Vamos et al[8] study is not dissimilar to the control arm of the CARE-HF (Cardiac Resynchronization-Heart Failure) study (30% at 30 months).[10] Furthermore, we know that the complication rate for upgrade or lead revision procedures is higher than that for de novo implants and was 18.7% in the REPLACE registry.[11,12] The CARE-HF population was not quite the same as the upgrade population in Vamos et al, but the question needs to be asked: if the absolute benefit of CRT is as low as 16% and the complication rate of an upgrade as high as 19%, are we providing any net benefit to the heart failure population as a whole when we perform upgrade procedures and could we even be guilty of verschlimmbesserung?

The answer is probably not. We know that right ventricular (RV) pacing increases the risk of heart failure hospitalization in patients with sinus node disease[13] and the risk of hospitalization and death in patients who do not have a bradycardia indication for an ICD.[14] Despite the relatively high number of complications seen in CRT upgrade procedures, only a small

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proportion of these are serious or cause long-term problems.[12] So we know that heart failure patients with a bradycardia indication for a device do not do well with simple pacemakers or ICDs, and we also know that the risk of a prognostically important complication from a device upgrade is small but is doing something better than doing nothing?

The answer is probably yes! There are several small randomized crossover studies with up to 6 months of CRT compared with up to 6 months of RV pacing that have shown symptomatic improvement, less hospitalization, and improved cardiac function during the CRT phase of the studies.[6] The European Cardiac Resynchronization Therapy Survey compared 1675 de novo CRT implants with 692 upgrade procedures and found no difference in the frequency of periprocedural complications and 1-year mortality. The same study showed similar improvements in NYHA class and reduction in QRS duration in the 2 groups. BLOCK HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block)[15] showed that CRT in patients with a bradycardia indication for a device and mildly impaired systolic function but not fulfilling standard indications for CRT, reduced the combined end point of death or heart failure hospitalization. This is relevant to the Vamos et al[8] study upgrade population as we can surmise, given the baseline characteristics of these patients, that a significant proportion would have fulfilled the entry criteria for BLOCK HF when they had their original device implanted. Perhaps one of the reasons that the upgrade population outcomes do not seem to be as good as the de novo population in Vamos et al is that they received their CRT upgrade too late in their disease course and may have responded better had there not been such a significant deterioration in their cardiac and overall health state. This is consistent with the finding of Chang et al[16] that a pre-CRT upgrade LV ejection fraction ≥43.5% predicts echocardiographic reverse remodeling in upgrade patients.

Although there are multitudes of small randomized crossover studies, controlled studies, and observational studies suggesting the benefit of CRT upgrade, there is a need for large, high-quality randomized study data to confirm that upgrading to CRT confers overall benefit. Foley et al[17] found no difference in outcome in patient's upgraded to CRT compared with de novo implant patients in a controlled study. The authors concluded that, "Proof of a benefit from upgrading to CRT requires a randomized comparison with RV-paced patients with heart failure who are not upgraded to CRT. On the basis of emerging evidence of the deleterious effects of RV pacing, however, it seems unlikely that such a study will ever be undertaken."

Fortunately, BUDAPEST-CRT[18] is one such prospective, multicenter randomized study that is underway. The investigators aim to randomize 360 heart failure patients with a pacemaker or ICD in situ and LV ejection fraction ≤35%, paced QRS ≥150 ms, and RV pacing ≥20% to CRT-D or ICD. Patients will be followed for 12 months to confirm the benefits or otherwise of CRT upgrade procedures.

While we await high-quality randomized data, we need to choose our upgrade patients wisely. We need to take into consideration the risks of LV lead placement, the reduced service life of biventricular devices and, most importantly, which patients are most likely to benefit. We need to work out which study populations most closely resemble a specific patient and decide whether the probability of benefit outweighs the procedural risk. In addition, we have to consider the expense of CRT upgrades. De novo CRT-D and CRT-P implantation seems to meet the $50 000/QALY benchmark often used for healthcare interventions in the United States,[19] but such economic calculations are based on highly selected patients of the large randomized controlled CRT trials. Recent data with quadripolar leads[20] may favorably affect such cost–benefit analyses, but it is not clear that CRT upgrade patients with more comorbidities and possibly a lower chance of response are as likely to meet willingness-to-pay thresholds even if they fulfill guideline criteria. The decision to perform a CRT upgrade is not a simple one.

Disclosures

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