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EDITORIAL COMMENT

Cardiac resynchronization therapy; the importance of evaluating cardiac metabolism

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Cardiac resynchronization therapy (CRT) has shown to be an effective treatment for patients with advanced heart failure (HF) (NYHA Class III or IV), reduced left ventricular ejection fraction (LVEF $< 35\%$) and wide QRS complexes (>120 ms) [1, 2]. The beneficial effects include improvement in heart failure symptoms, exercise capacity, and left ventricular function, as well as less heart failure hospitalizations and lower mortality rates. Despite these remarkable results, 30–40% of patients show no benefit after CRT, the so-called 'non-responders' [3–5]. It remains, however, difficult to distinguish responders from non-responders in the early period after CRT. The presence of LV dyssynchrony prior to implantation and its subsequent reduction after implantation are proposed as the key mechanisms for response to CRT [5, 6].

A variety of imaging modalities has already been applied to identify dyssynchrony and to evaluate the effects of CRT [7–10]. The use of echocardiography [11–17], magnetic resonance imaging (MRI) [18–29], and multislice computed tomography (MSCT) [30–43] has recently been proven for patients eligible for CRT. In addition, nuclear imaging techniques have become suited for the evaluation of LV dyssynchrony [44–51]. Until now, scintigraphic studies in CRT mainly concerned radionuclide angiography with phase image analysis [52–55]. In recent years positron emission tomography (PET) has emerged as a suitable modality to study the metabolic mechanisms of left ventricular dyssynchrony and the effects of CRT [56]. It has been reported that dyssynchrony influences regional myocardial workload, cardiac efficiency and oxygen metabolism as measured by carbon-11 (11C)-acetate PET. Several studies did already report that 11C-acetate PET performed in the chronic phase after CRT showed improvement of oxygen metabolism and cardiac efficiency by CRT [57, 58]. However, there are no data regarding the value of 11C-acetate PET to predict responses to CRT in the acute phase after treatment.

In the current issue in the International Journal of Cardiovascular Imaging, Kitaizumi et al. [59] examined the usefulness of 11C-acetate PET for assessing the early efficacy of CRT in 20 patients with severe heart failure. All patients underwent 11C-acetate PET imaging within 1 week after CRT. Oxygen consumption was measured by the mono-exponential clearance rate of 11C-acetate for both the patient's own beats (CRT off) and biventricular pacing (CRT-on). Plasma brain natriuretic peptide (BNP) levels were measured at 1, 3 and 12 months after installment of

Editorial Comment to the article by Kitaizumi K, Yukiiri K, Masugata H et al. Acute Improvement of Cardiac Efficiency Measured by 11C-Acetate PET after Cardiac Resynchronization Therapy and Clinical Outcome (CAIM 1496)

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CRT. Oxygen consumption was measured by the mono-exponential clearance rate of 11C-acetate (Kmono) for both CRT-off and CRT-on. Cardiac efficiency was determined using the work metabolic index (WMI), which was calculated as WMI = (stroke volume index) × (systolic blood pressure) × (heart rate)/Kmono. Two groups of patients were discerned: 14 patients with improved cardiac efficiency and six patients with deteriorated cardiac efficiency by CRT-on. The mono-exponential clearance rate of 11C-acetate decreased significantly by CRT-on in the improved cardiac efficiency group, but increased in the deteriorated- cardiac efficiency group. At 1-year follow-up, there were significantly higher rates of major cardiac adverse events in the deteriorated cardiac efficiency group than in the improved-cardiac efficiency group. Consequently, the decrease in oxygen consumption in the early period after CRT is a useful marker for predicting a good clinical outcome after CRT. The most impressive result of the study was that the patients with improved cardiac efficiency showed decreased oxygen consumption indicating improved oxidative metabolism with no changes in hemodynamic parameters in the early period after CRT. The authors concluded that improvement of cardiac efficiency, as assessed by 11C-acetate PET in the early period after CRT, was produced by the decrease in oxygen consumption in patients showing good responses to CRT.

There are several caveats to the study, already recognized by the authors. Because of the relatively small population studied (20 patients), the authors were not able to address differences between non-ischemic (NICM) and ischemic (ICM) patients. These differences might be of importance, since Lindner et al. [60] showed that in patients with NICM CRT induces changes of myocardial oxygen consumption and myocardial blood flow on a regional level with a more uniform distribution between the myocardial walls and improved ventricular efficiency than in patients with ICM. Therefore, CRT might to be more effective in NICM than in ICM patients. Marsan et al. [61] questioned whether sequential biventricular pacing provides substantial benefits over conventional simultaneous stimulation, particularly regarding the differences between ICM and NICM patients. It was found that optimized sequential biventricular pacing further increased left ventricular systolic performance as compared to simultaneous stimulation; this finding held in particular for ICM patients where the presence of a large scar was correlated with a larger left ventricular pre-activation. So, ICIM and NICM patients should be separately considered in the evaluation of the effects of CRT therapy. Next, the PET studies were performed only once in the early period after CRT and not in the chronic phase. Comparison of PET data between acute and chronic phases may have more clearly shown the clinical use of PET to predict patient responses to CRT. However, the present results provide new information by showing that improved cardiac efficiency due to decreased oxygen metabolism may predict the improvement of cardiac function assessed by plasma BNP levels as well as predicting major adverse cardiac events after CRT.

To summarize, the study by Kitaizumi et al. [59] clearly shows that improvement of cardiac efficiency assessed by 11C-acetate PET in the early period after CRT is caused by a decrease in oxygen consumption in patients who showed an adequate response to CRT. The decrease in oxygen consumption assessed by PET in the early period after CRT is therefore a potential marker to predict improvement of cardiac function and major cardiac events during the first year of follow-up. More metabolic cardiac studies are needed to unravel the basic mechanisms of left ventricular dyssynchrony in order to install the most appropriate therapy [62, 63].

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