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Review

Current concepts relating coronary flow, myocardial perfusion and metabolism in left bundle branch block and cardiac resynchronisation therapy

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ABSTRACT

Cardiac resynchronisation therapy (CRT) improves mortality and symptoms in heart failure patients with electromechanically dyssynchronous ventricles. There is a 50% non-response rate and reproducible biomarkers to predict non-response have not been forthcoming. Therefore, there has been increasing interest in the pathophysiological effects of dyssynchrony particularly focusing on coronary flow, myocardial perfusion and metabolism. Studies suggest that dyssynchronous electrical activation effects coronary flow throughout the coronary vasculature from the epicardial arteries to the microvascular bed and that these changes can be corrected by CRT. The effect of both electrical and mechanical dyssynchrony on myocardial perfusion is unclear with some studies suggesting there is a reduction in septal perfusion whilst others propose that there is an increase in lateral perfusion. Better understanding of these effects offers the possibility for better prediction of non-response. CRT appears to improve homogeneity in myocardial perfusion where heterogeneity is described in the initial substrate. Novel approaches to the identification of non-responders via metabolic phenotyping both invasively and non-invasively have been encouraging. There remains a need for further research to clarify the interaction of coronary flow with perfusion and metabolism in patients who undergo CRT.

1. Introduction

Heart failure is a complex clinical syndrome that is associated with a significant morbidity, mortality and socio-economic burden due to an increasingly elderly population. Many heart failure patients have electrically dyssynchronous ventricular contraction and abnormal atrioventricular coupling which impair the ability of the ventricle to fill with or eject blood. This abnormal electrical activation manifests on the surface electrocardiogram as broadening of the QRS complex and lengthening of the PR interval. Cardiac resynchronisation therapy (CRT) with atriobiventricular pacing aims to optimise ventricular function through resynchronisation of the atrioventricular, interventricular and intraventricular contraction timings. CRT has been shown to offer prognostic as well as symptomatic benefit in selected patients with evidence of severe LV dysfunction and electrical ventricular dyssynchrony. Although morbidity and mortality are reduced with CRT, the number of non-responders remains at 30–50% [1]. Attempts to determine patient characteristics that may further improve selection for CRT have proven elusive with measures often showing potential but their validity has not been reproducible [2].

This failure to easily identify non-responders pre-implantation has led to increasing interest in the pathophysiological mechanisms that underlie electrical and mechanical dyssynchrony in heart failure. One aspect of this is a renewal in interest in the importance of myocardial perfusion to CRT response and its relationship with any concomitant metabolic abnormalities. Previous studies suggested CRT offered an increase in global contractility without an increase in overall myocardial work or oxygen consumption [3]. However a recent study has suggested that myocardial oxygen consumption does increase with CRT but that the corresponding increase in contractility is relatively much greater resulting in an improvement in overall myocardial efficiency [4]. Furthermore, experimental work in the canine model suggests that response to CRT is dependent on a minimal myocardial perfusion [5]. Perfusion below this threshold, which lies within pathophysiological levels seen in the clinical setting, seems to preclude a favourable response to CRT.

Therefore, the role of myocardial perfusion in CRT appears to be a relevant area of inquiry and one of the elements that needs to be understood in the search for accurate criteria to predict CRT response. Furthermore increasingly accurate descriptions of metabolic changes

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associated with heart failure and electromechanical dyssynchrony are beginning to show promise in the prediction of non-response.

This review will examine the experimental data that has assessed the effects of electromechanical dyssynchrony on myocardial perfusion, coronary flow and myocardial metabolism before considering the effect CRT has on these indices.

Subsequently, the expanding role of computer modelling and the potential clinical application of novel metrics to allow patient specific assessment of CRT response pre-implantation will be analysed. A call for further research and suggestions as to the shape such studies should take concludes the article. The key messages are summarised in Table 1.

1.1. Effect of ventricular dyssynchrony on myocardial perfusion and coronary flow

There are three common patterns of ventricular electrical dyssynchrony which are found on the surface ECG: LBBB, right bundle branch block and non-specific intraventricular conduction defect. There has been a wealth of research into the assessment of the coronary circulation and myocardial perfusion in patients with LBBB. This is due to the particularly marked positive response of these patients to CRT and also the significant historical interest in "false positive" non-invasive tests for inducible ischaemia in this cohort [6]. The assessment of patients with LBBB will form the focus of this review. LBBB represents a delay in electrical and accordingly mechanical activation of the left ventricle resulting in inter- and intraventricular dyssynchrony.

Early work by Delhaas et al. in a canine model paced from different ventricular sites, demonstrated significantly reduced regional oxygen uptake and regional blood flow in early activated areas of myocardium compared with late activated areas [7]. This was refined in a canine model, where septal hypoperfusion was linked with a reduction in the systolic circumferential shortening following left bundle branch ablation [8]. The model also demonstrated an increase in myocardial blood flow to the lateral wall in conjunction with an increase in systolic circumferential shortening in that region. These findings suggest that the reduction in myocardial blood flow to the septum may be a result of reduced septal workload and conversely that the increase in myocardial blood flow to the lateral wall is a result of an increased workload. Such findings suggest a physiological rather than pathological response. Further work by Vernooy et al. demonstrated that these regional differences disappeared following the application of CRT [9].

Studies that assessed the effects of ventricular electromechanical dyssynchrony on myocardial perfusion and metabolism in man have largely obtained data from nuclear imaging. Initial investigation of patients with LBBB suggested that there was relative hypoperfusion in the septum compared with the lateral wall of the left ventricle even in patients with normal coronary arteries and these findings have been replicated on many occasions [10,11].

Table 1
Review Highlights

Key messages
• Understanding the pathophysiology of electromechanical dyssynchrony may help to predict patients who will respond to CRT.
• Electromechanical dyssynchrony alters coronary blood flow and myocardial perfusion and metabolism. It is unclear if such changes are a physiological or pathophysiological response.
• Experimental data comes from small studies and is inconsistent.
• Recent studies demonstrate there may be a role for the assessment of physiological indices such as coronary flow reserve prior to CRT implantation however multicentre, randomised trials are required.
• Future experimental research should focus on patients with Class 2a and Class 2b indications for CRT and patients with ischaemic cardiomyopathy.
• Computer modelling may well support such future research as it has the ability to assess certain physical properties that are difficult to measure in vivo.

More recent quantitative research has demonstrated an increase in global myocardial blood flow during rest and exercise in presumed non-ischaemic patients with LBBB when compared with patients without electrical dyssynchrony [12]. This increase in myocardial perfusion, particularly in the lateral wall during exercise, accords more with Delhaas' and Vernooy's findings in the canine model and may be a reflection of increased myocardial oxygen demand due to inefficient cardiac mechano-energetics induced by dyssynchronous electrical activation. The rationale for this is that, in a normal left ventricle (LV), all myocardial segments are activated almost simultaneously and contract synchronously. This results in both septal and lateral annuli being pulled towards the stationary LV apex. However, in LBBB, the septum is activated first and whilst it is developing a contractile force and shortening, the contralateral wall is passive. This exerts a pulling effect on the latent opposite wall. The combination of unloaded contraction of the septum, stretching the lateral wall, followed by delayed lateral wall contraction, which then stretches the septum, leads to an overall greater workload, particularly for the lateral wall. This is reversed when CRT is applied resulting in homogenisation of work across the ventricle.

Koepfli's study also demonstrated reversible relative hyperperfusion in the lateral wall of patients with reversible LV dyssynchrony during right ventricular (RV) pacing compared with their intrinsic rhythm. Thus rather than LBBB causing septal hypoperfusion it is possible that LBBB causes lateral wall hyperperfusion.

Koepfli studied "spontaneous" LBBB patients and makes no reference to the patients' LV systolic function. This limits extrapolation of these findings to the CRT heart failure population. For patients who have developed LV impairment as a result of chronically high percentages of right ventricular pacing are likely to have undergone cellular and metabolic changes not found in those with LBBB without heart failure [13]. Indeed, longer term RV apical pacing has been shown to result in myocardial perfusion defects in variable locations within the ventricle [14]. The incidence and size of these perfusion defects increases with time. They are associated with apical wall motion abnormalities and a reduction in left ventricular ejection fraction.

Koepfli's work is alone in studies on man suggesting that there is lateral wall hyperperfusion rather than septal hypoperfusion. In spite of the above criticisms, this quantitative assessment of both coronary flow and myocardial perfusion suggesting lateral wall hyperperfusion on exertion offers a different explanation to the septal hypoperfusion hypothesis examined above.

The theory that dyssynchrony may alter regional myocardial work is supported by Masci et al. who found using Positron emission Tomography (PET) that patients with LBBB and reduced ejection fraction had a higher myocardial glucose metabolism in the lateral wall compared with the septum when compared with a group of non-dyssynchronous patients with non-ischaemic cardiomyopathy [15]. This suggests that a heterogeneous shift in the LV regional workload due to dyssynchrony results in alterations in the regional myocardial metabolic demand. The extra metabolic load as a result of dyssynchronous LV contraction can in theory lead to higher demand on global myocardial perfusion. However, Masci found no consistent changes in myocardial perfusion to either confirm or refute this theory.

Skalidis et al. demonstrated, in an invasive setting, that the time to maximum peak diastolic flow velocity was significantly longer in the left anterior descending (LAD) coronary artery of patients with LBBB and perfusion defects compared with normal subjects [16]. This observation coupled with the associated reduction in coronary flow reserve (CFR) suggests that dyssynchrony can have a deleterious effect on the myocardial microvascular circulation. Interestingly, Koepfli also noted a reduction in the CFR in the septum of patients with LBBB. Skalidis et al. postulated that an increase in early diastolic compressive resistance resulting from delayed ventricular relaxation in LV dyssynchrony resulted in an impairment of early diastolic blood flow in the LAD. The authors further demonstrated that CFR was similarly reduced in