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# Changes in contractility determine coronary haemodynamics in dyssynchronous left ventricular heart failure, not vice versa

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ABSTRACT

*Background:* Biventricular pacing has been shown to increase both cardiac contractility and coronary flow acutely but the causal relationship is unclear. We hypothesised that changes in coronary flow are secondary to changes in cardiac contractility. We sought to examine this relationship by modulating coronary flow and cardiac contractility.

*Methods:* Contractility and lusitropy were altered by varying the location of pacing in 8 patients. Coronary autoregulation was transiently disabled with intracoronary adenosine. Simultaneous coronary flow velocity, coronary pressure and left ventricular pressure data were measured in the different pacing settings with and without hyperaemia and wave intensity analysis performed.

*Results:* Multisite pacing was effective at altering left ventricular contractility and lusitropy (pos. $dp/dt_{max}$ −13% to +10% and neg. $dp/dt_{max}$ −15% to +17% compared to baseline). Intracoronary adenosine decreased microvascular resistance (362.5 mm Hg/s/m to 156.7 mm Hg/s/m, $p < 0.001$) and increased LAD flow velocity (22 cm/s vs 45 cm/s, $p < 0.001$) but did not acutely change contractility or lusitropy. The magnitude of the dominant accelerating wave, the Backward Expansion Wave, was proportional to the degree of contractility as well as lusitropy ($r = 0.47$, $p < 0.01$ and $r = -0.50$, $p < 0.01$). Perfusion efficiency (the proportion of accelerating waves) increased at hyperaemia (76% rest vs 81% hyperaemia, $p = 0.04$). Perfusion efficiency correlated with contractility and lusitropy at rest ($r = 0.43$ & $-0.50$ respectively, $p = 0.01$) and hyperaemia ($r = 0.59$ & $-0.6$, $p < 0.01$).

*Conclusions:* Acutely increasing coronary flow with adenosine in patients with systolic heart failure does not increase contractility. Changes in coronary flow with biventricular pacing are likely to be a consequence of enhanced cardiac contractility from resynchronization and not vice versa.



## 1. Introduction

### 1.1. Background

Cross-talk between the coronary vasculature and cardiac muscle has been proposed as a theory to understand the simultaneous effects of coronary blood flow on cardiac contractility and vice versa [1].

Reduced coronary flow in the Left Anterior Descending (LAD) Artery and corresponding perfusion defects have been noted in patients with dyssynchronous left ventricular activation [2–4]. Furthermore, Cardiac Resynchronization Therapy (CRT) has been shown to increase LAD flow and correct these perfusion defects [5]. It is unclear whether the observed increases in LAD flow are a bystander effect of electrical resynchronization or whether the increase in coronary flow is mechanistically important in mediating some of the physiological effects of CRT, resulting in the recruitment of hibernating myocardium [6,7].

Coronary wave intensity can be calculated from simultaneously acquired coronary flow and pressure measurements. It provides temporal information on the nature and origin of forces that drive and impede myocardial perfusion [8]. This makes it an ideal tool to investigate cardiac-coronary coupling, specifically the relationship between changes in LAD flow, acute left ventricular (LV) contractility and electrical activation. Typically, as many as six waves have been described with the vast majority of flow being driven by a dominant backward travelling expansion wave (BEW) that "sucks" blood through the coronary artery and a dominant forward compression wave (FCW) which derives from the ejection of blood from the left ventricle into the aorta

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and down the coronary arteries [8,9]. The effect of changes in both contractility and microvascular resistance on coronary wave energy have previously been studied in a canine model and used to identify the causes of the systolic impediment to coronary flow velocity [10]. Kyriacou et al. demonstrated in a group of patients with CRT that an acute increase in contractility was associated with an increase in the BEW in the left main coronary artery [11]. This is the only clinical study to date where coronary wave energy and coronary flow have been correlated with changes in acute LV contractility. Contractility and microvascular resistance have not previously been *simultaneously* modulated in humans and hence their relative impact on wave energy remains unclear.

### 1.2. Hypothesis

We hypothesised that increased LAD coronary flow with hyperaemia would not affect LV contractility. We also sought to characterise the relationship between changes in acute LV contractility and lusitropy with the dominant wave energies driving coronary flow velocity in patients with dyssynchronous heart failure.

## 2. Methods

### 2.1. Study design and patient population

We investigated a group of patients with a CRT device as a clinical model that allowed manipulation of both coronary blood flow and contractility. Patients who had been implanted with a CRT device and were known to have unobstructed coronary arteries at invasive angiography were invited to take part.

Cardiac contractility and lusitropy were altered by pacing from different points in the left and right ventricles. The first derivative of LV pressure was used to assess contractility and relaxation (pos. $dp/dt_{max}$ and neg. $dp/dt_{max}$ respectively). Microvascular resistance was altered by inducing hyperaemia with intracoronary adenosine.

The study received approval from the Local Research Ethics Committee (Rec no. 11/LO/1232) and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent prior to taking part in the study.

### 2.2. Invasive protocol

Patients received dual antiplatelet therapy prior to the procedure and received unfractionated heparin to keep an activated clotting time > 250 s. Arterial access was gained via femoral and radial arteries. A 0.014″ Doppler wire (ComboWire™ model 9500, Volcano Corporation) was advanced to the proximal LAD to make simultaneous measurements of intracoronary pressure and Doppler flow velocity. A Primewire (Volcano Corporation) was placed in the LV cavity to measure pos. $dp/dt_{max}$ and neg. $dp/dt_{max}$.

Acute contractility was modulated by pacing the ventricle from different points using the in situ CRT device. The site of ventricular stimulation was altered allowing atrio-ventricular synchronous pacing from the right ventricle alone, the left ventricle alone and biventricularly via the epicardial pacing lead. In 5 of the 8 patients, we also used a roving endocardial pacing catheter to perform LV endocardial pacing, which additionally allowed atrial synchronous biventricular endocardial pacing (with both a septal and lateral position used for the endocardial component) and simultaneous right ventricular endo, LV endo and LV epicardial pacing. All studies were performed with pacing at 10 beats above the intrinsic atrial rate to control for the Bowditch effect [12]. An atrially paced, ventricular sensed rhythm was used as the baseline in patients with in tact AV nodes. An atrially paced, right ventricular paced rhythm was used as the baseline in patients with AV block.

Intracoronary adenosine was given as a bolus dose of 36 microgrammes to induce hyperaemia, at each pacing protocol.

### 2.3. Data selection and beat analysis

The first three to five beats recorded after a change in pacing protocol were selected for analysis according to our previously published protocol [13]. A period of at least 10 s was allowed for stabilisation with each new pacing parameter.

### 2.4. Wave intensity analysis

Signals were sampled at 200 Hz and the raw data was exported to a custom-made study manager programme (Academic Medical Center, Amsterdam, Netherlands) for data extraction of selected beats at each different condition. Wave intensity analysis was then applied to the coronary data using custom-made software, "Cardiac Waves" (King's College London, London, United Kingdom). Details of the methodology used to perform wave intensity analysis have been previously described [14]. Briefly, a Savitzky–Golay convolution method was adopted using a polynomial filter to refine the derivatives of the intracoronary pressure and velocity signals. The selected three to five consecutive cardiac cycles were gated to the ECG R wave peak, with ensemble averaging of aortic pressure, distal coronary pressure (Pd), Average Peak velocity (APV) and heart rate. Net coronary wave intensity (dI) was calculated from the time derivatives (dt) of ensemble-averaged coronary pressure and flow velocity (U) as follows: $dI = dPd/dt \times dU/dt$. Net wave intensity was then separated into forward and backward components.

The area beneath the 4 most prominent wave intensity peaks identified were analysed and included in this article. These are 1) the positive, aorta-derived FCW, occurring at the onset of systole, 2) the negative backward compression wave (BCW) also occurring at the onset of systole, 3) the negative BEW, the first backward wave occurring after the onset of ventricular relaxation, identified by the onset of diastole and 4) the positive Forward Expansion Wave (FEW) (see Fig. 1).

Coronary Flow Velocity Reserve was calculated as the ratio between APV at rest and hyperaemia. Microvascular resistance (MR) was calculated as the ratio of the Pd and APV.

We also calculated coronary perfusion efficiency (P.E). This is a metric which quantifies accelerating wave energy as a proportion of total coronary wave energy generated by the FCW and BEW which are the waves that theoretically drive rather than impede coronary flow

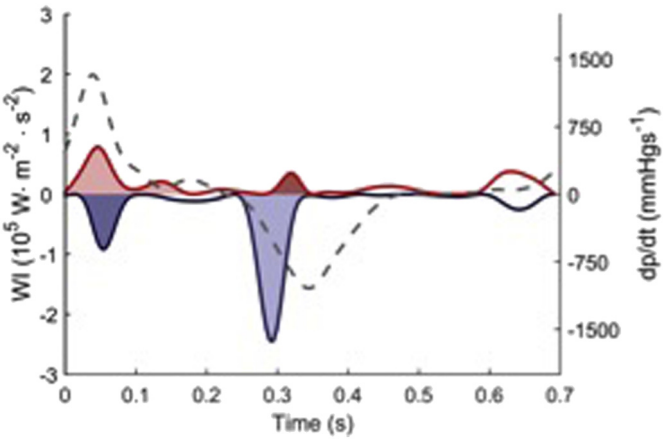


**Fig. 1.** Wave intensity analysis of a single heartbeat. Forward waves are red and backward waves are blue. The accelerating waves (BEW and FCW) are shaded light and the decelerating waves (BCW, FEW) are shaded dark. The hatched black line corresponds to changes in LV pressure on the right hand axis.