Coronary Wave Energy
A Novel Predictor of Functional Recovery After Myocardial Infarction

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Background—Revascularization after acute coronary syndromes provides prognostic benefit, provided that the subtended myocardium is viable. The microcirculation and contractility of the subtended myocardium affect propagation of coronary flow, which can be characterized by wave intensity analysis. The study objective was to determine in acute coronary syndromes whether early wave intensity analysis-derived microcirculatory (backward) expansion wave energy predicts late viability, defined by functional recovery.

Methods and Results—Thirty-one patients (58±11 years) were enrolled after non-ST elevation myocardial infarction. Regional left ventricular function and late-gadolinium enhancement were assessed by cardiac magnetic resonance imaging, before and 3 months after revascularization. The backward-traveling (microcirculatory) expansion wave was derived from wave intensity analysis of phasic coronary pressure and velocity in the infarct-related artery, whereas mean values were used to calculate hyperemic microvascular resistance. Twelve-hour troponin T, left ventricular ejection fraction, and percentage late-gadolinium enhancement mass were 1.35±1.21 µg/L, 56±11%, and 8.4±6.0%, respectively. The infarct-related artery backward-traveling (microcirculatory) expansion wave was inversely correlated with late-gadolinium enhancement mass (r=–0.81; P<0.0001) and strongly predicted regional left ventricular recovery (r=0.68; P=0.001). By receiver operating characteristic analysis, a backward-traveling (microcirculatory) expansion wave threshold of 2.8 W m–2 s–2×105 predicted functional recovery with sensitivity and specificity of 0.91 and 0.82 (AUC 0.88). Hyperemic microvascular resistance correlated with late-gadolinium enhancement mass (r=0.48; P=0.03) but not left ventricular recovery (r=–0.34; P=0.07).

Conclusions—The microcirculation-derived backward expansion wave is a new index that correlates with the magnitude and location of infarction, which may allow for the prediction of functional myocardial recovery. Coronary wave intensity analysis may facilitate myocardial viability assessment during cardiac catheterization. (Circ Cardiovasc Interv. 2013;6:166-175.)

Key Words: acute coronary syndromes ■ left ventricular remodeling ■ microvascular function ■ myocardial viability ■ wave intensity analysis

Coronary revascularization improves mortality and morbidity after an acute myocardial infarction, provided that the myocardium subtended by the diseased artery is viable.1,2 Non-ST elevation myocardial infarction (NSTEMI) accounts for two thirds of all acute myocardial infarction presentations3 and is usually treated by initial pharmacological stabilization followed by coronary angiography with a view to revascularization, ideally within 96 hours of symptom onset.4,5 This expedited treatment algorithm is designed to reduce the risk of recurrent myocardial infarction, but, as a consequence, most patients do not undergo noninvasive assessment of left ventricular function and/or myocardial viability before cardiac catheterization. At present, there are no invasive tools for assessing myocardial viability in the catheterization laboratory, as an adjunct to coronary angiography. A real-time invasive physiological index of viability would enable personalized and instantaneous risk stratification after acute coronary syndromes (ACS), with revascularization targeted to those who are likely to derive long-term benefit.
An important determinant of myocardial viability and tissue perfusion is the integrity of the microcirculation. The severity of microvascular dysfunction influences left ventricular (LV) functional recovery, cardiovascular morbidity, and mortality after ACS. The advent of pressure and Doppler sensor-tipped guide wire technology has allowed detailed in vivo interrogation of microcirculatory physiology, and these techniques have demonstrated that microcirculatory compromise correlates with infarct size after ST-elevation myocardial infarction (STEMI). Wave intensity analysis (WIA) of phasic coronary pressure and flow profiles has allowed further characterization of the microcirculation and its impact on coronary flow in a number of stable clinical settings. These studies demonstrate that mechanical impedance of the coronary microcirculation by the myocardium is the predominant factor that governs myocardial perfusion, with a backward-traveling (microcirculatory) expansion wave (BEW) identified as being the most influential in generating diastolic coronary flow. WIA has not been used previously to assess the effect of myocardial infarction on the energy transfer within the coronary circulation.

The aims of our study are to assess the correlation between microcirculatory wave energy and the extent of myocardial infarction and to assess the use of this novel physiological index to predict recovery of ventricular function after revascularization. We also compared the BEW with hyperemic microvascular resistance (hMR), the invasive reference standard for measuring microvascular function.

**Methods**

**Study Population**

Patients scheduled to undergo urgent coronary angiography and revascularization 2 to 7 days after presenting with an NSTEMI, defined as symptoms of ischemia lasting 220 minutes (chest pain score >4) in conjunction with significant elevation in cardiac biomarkers (defined as a troponin T [TnT] >0.20 μg/L) identified 12 hours after symptom onset, were eligible for inclusion into the study. To ensure that cardiac magnetic resonance imaging findings reflected acute myocardial injury, patients were not enrolled if they had experienced a previous myocardial infarction. Additional exclusion criteria were a previous diagnosis of valvular disease, previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery, an occluded infarct related artery (IRA) at time of angiography, persistent arrhythmias, or hemodynamic instability. Patients with contraindications to cardiac magnetic resonance imaging (CMR) at study entry, such as pacemakers, implantable defibrillators, claustrophobia, or metallic intracranial implants, were also excluded.

**Cardiac Catheterization and Intracoronary Measurements**

All of the patients were preloaded with aspirin (300 mg) and clopidogrel (600 mg). Interventional cardiologists performing the catheterization procedures were blinded to the information obtained from the preceding CMR. Coronary angiography was performed using a standard Judkins technique. Intracoronary nitroglycerin was administered before diagnostic angiography and intracoronary physiological measurements. Identification of the IRA was based on the presenting 12-lead ECG and angiographic findings. Hemodynamic measurements were obtained in the IRA immediately after PCI. Measurements were then carried out in an angiographically normal reference coronary artery (with <10% diameter stenosis), supplying a myocardial territory remote to the infarct region. All of the measurements were obtained during intracoronary adenosine induced hyperemia (≥60 μg for right and 96 μg for left coronary arteries, respectively). Aortic pressure was measured via the coronary guiding catheter. Intracoronary pressure (P) and average peak velocity (APV) were measured via a 0.014-inch dual pressure-Doppler sensor guide wire (CoroWire Volcano Corp San Diego, California), with the tip being positioned in the distal vessel. Simultaneous pressure and Doppler measurement were repeated ≥3 times in each location and condition to reduce acquisition error.

**Hemodynamic Data Analysis**

**Phasic Pressure and Flow**

Data were sampled at 250 Hz and analyzed offline using a customized program developed on Matlab (Mathworks, Inc, Natick, MA). A Savitzky–Golay convolution method was adopted, using a polynomial filter to refine the derivates of the aortic pressure and velocity signals. Three to 6 consecutive cardiac cycles were selected for resting and hyperemic conditions, gated on the ECG R wave peak, with ensemble averaging of aortic pressure, PAP, APV, and heart rate. For the purposes of WIA, it has been considered that diastole commences with the onset of ventricular relaxation, signified by the dichotic notch on the arterial pressure waveform, as described previously. Net coronary wave intensity (dI) was calculated from the time derivatives (dt) of ensemble-averaged coronary pressure and flow velocity (U) as follows: dI = dP /dt/dU/dt. Coincident (microcirculation-derived) backward and (aorta-derived) forward propagating waves were separated assuming blood density to be 1050 kg/m³ and estimating coronary wave speed using the sum of squares method. The peak energy (in W m⁻² s⁻¹ x10⁵) carried by the 3 most prominent wave energies identified were analyzed and included in this article. These were the positive, forward-directed (aorta-derived) compression wave (FCW), occurring at the onset of systole, the concurrently occurring negative (backward, microcirculation-derived) compression wave (BCW), and the backward expansion waves (BEW), the first negative wave occurring at the onset of ventricular relaxation, identified by the onset of diastole (Figure 1). The investigators who performed the data analyses were blinded to all of the clinical patient data.

**Mean-per-Beat Pressure and Flow**

hMR was calculated as the ratio of mean PAP (mm Hg cm⁻¹ s) during maximal hyperemia, obtained through simultaneous intracoronary pressure-flow measurements, during 3 to 6 consecutive cardiac cycles.
Cardiac Magnetic Resonance Imaging

Index CMR studies were performed before emergent angiography and PCI. The scans were performed on a dedicated 3-Tesla cardiac magnetic resonance imaging scanner (Achieva, Philips Healthcare, Best, the Netherlands) equipped with dual-radio-frequency transmission technology and a 32-channel phase array body coil. Cine images were acquired using a standard steady-state free precession cine technique in 2-, 3-, and 4-chamber orientations and in an LV short-axis stack covering the LV from apex to base. The acquisition pulse sequence provided a typical spatial resolution of 1.8×1.8×8 mm with a 2-mm interslice gap and a temporal resolution of 50 frames per second. Late gadolinium-enhanced (LGE) imaging was performed using an inversion recovery fast gradient echo sequence 15 to 20 minutes after the intravenous administration of 0.2-mmol/kg body weight of gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) to ensure optimized infarct delineation in the ACS setting. A stack of images was acquired in the same LV short-axis orientation as the cine images to ensure registration between cine CMR and infarct measurements. LGE acquisition was guided by a Look-Locker sequence with a typical prepulse delay of 200 to 330 ms. Follow-up scans were performed between 3 and 4 months, using an identical acquisition protocol.

CMR Analysis

Quantitative analysis was performed offline, by blinded observers, using dedicated CMR viewing software (CMR 42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). The area of hyperenhancement was quantitatively determined using a previously described signal intensity method, where infarcted tissue is defined as an area of myocardium with LGE signal intensity >5 SDs compared with a region of interest in an area of remote normal myocardium (Figure 2A and 2B). Endo- and epicardial contours were drawn (excluding papillary muscles) to derive total LV mass. Infarct mass was expressed as the absolute mass of infarcted tissue (in grams) and as the percentage of the total LV mass.

Quantification of regional wall thickening was performed as described previously (Figure 2C and 2D). Briefly, endocardial and epicardial contours in diastole (first image of the cine series) and systole (identified as the phase with smallest LV volume) were drawn for the entire ventricular cavity. The area of infarction on the cine images was identified by comparing the identical corresponding LGE images. Percentage of wall thickening was automatically calculated by determining the absolute differences in wall thickness between end diastole and end systole. Recovery of function after revascularization was defined as the percentage of change in regional wall thickening (%WT) in the infarct area, at follow-up, compared with the index study. Significant recovery in function postrevascularization was characterized as an increase in regional WT by ≥30% (%WT), identifying likely clinically relevant ventricular remodeling.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20. Correlation analysis was used to quantify the relation between WIA-derived separated wave energies and infarct size and recovery in function after PCI. Continuous variables were compared between groups, using the Wilcoxon signed-rank test and the Mann–Whitney test for paired or unpaired comparisons, respectively. A 2-tailed test for significance was performed in all of the analyses; \( P \leq 0.05 \) was considered statistically significant. Coefficient of variability analysis of the Doppler-pressure measurements was performed on the constituent pressure and velocity components, \( P \) and \( APV \), along with the microvascular resistance surrogate, \( hMR \). Coefficient of variability was calculated as the SD of the differences divided by the mean in 2 consecutively obtained data sets. Interobserver reproducibility for these measures was assessed using a single measure intraclass correlation coefficient. Percentage of recovery in ventricular function was assessed according to whether ≥30% recovery in regional wall thickening was observed after PCI. Using this characterization, receiver-operator characteristic analysis was performed to determine a cutoff value with maximal diagnostic accuracy for diastolic microcirculatory wave intensity (BEW) and \( hMR \), in predicting regional recovery in function, with the difference between the 2 indices assessed using the Delong receiver-operator characteristic comparison analysis. Data are presented as median with 25% to 75% interquartile ranges, unless otherwise specified.

Ethical Approval

The study protocol was approved by the institutional research ethics committee. All of the participants were provided with an information sheet detailing the study protocol before obtaining informed consent.
Results

Baseline Characteristics
Thirty-one patients with NSTEMI were recruited to the study, with 9 subsequent exclusions: 3 for claustrophobia during CMR, 2 requiring surgical revascularization, 1 for inadequate quality of Doppler-pressure trace, and 3 for neither CMR or angiographic features of an ACS. Twenty-two (18 men, 57 years of age [51–67 years]) completed both the CMR and intracoronary pressure and Doppler measurements, after enrollment 48 hours (48–78 hours) after symptom onset. Twelve-hour Troponin T was 1.35 µg/L (0.40–1.21 µg/L).

Quantitatively determined percentage diameter stenosis of the culprit lesion was 78% (71% to 88%) in the IRA (Table 1). Patients were scanned 3 hours (1–5 hours) before angiography (2 days [2–3 days] after symptom onset). LV ejection fraction was 56% (31% to 68%), and hyperenhanced infarct mass was 7.6 g (2.6–11.2 g), which corresponded with 7.1% (2.6–11.3%) of total LV mass (Table 2). Both parameters of infarct size, mass, and percentage of LV mass correlated linearly with TnT ($R=0.61$, $P=0.003$ and $R=0.67$, $P=0.001$, respectively, for the IRA BCW and $R=0.31$, $P=0.01$ and $R=−0.56$, $P=0.01$, respectively, for the IRA FCW).

In contrast, reference microcirculatory energy (BEW) did not correlate with either TnT or LGE mass ($R=0.02$, $P=0.46$, and $R=0.10$, $P=0.65$) and BCW ($R=−0.31$, $P=0.17$, $R=−0.007$, $P=0.97$, respectively). Similarly, no correlation was present with reference FCW ($R=−0.36$, $P=0.10$ and $R=−0.05$, $P=0.80$, respectively).

LV ejection fraction was proportional to the IRA aorta-derived systolic FCW ($R=0.55$, $P=0.008$, respectively) and, to a lesser extent, the distally originating systolic BCW ($R=0.43$; $P=0.04$). The diastolic BEW showed no such relationship ($R=0.23$, $P=0.30$).

Hyperemic Microvascular Resistance
hMR ($P_d/APV$) in the IRA was 2.34 mm Hg cm$^{-1}$ s (1.73–2.93 mm Hg cm$^{-1}$ s) compared with 1.90 mm Hg cm$^{-1}$ s (range, 1.52–2.59 mm Hg cm$^{-1}$ s) in the reference vessel ($P=0.001$). IRA hMR directly correlated with both TnT release ($R=0.46$, $P=0.04$) and LGE infarct mass ($R=0.48$, $P=0.03$). Reference hMR showed no correlation with either marker of infarct size (TnT, $R=0.31$, $P=0.18$ or LGE, $R=0.22$, $P=0.23$, respectively).

Variability and Interobserver Reproducibility
APV, $P_d$, and hMR had a coefficient of variability of 8.7%, 2.7%, and 7.3%, respectively. The single-measure intraclass coefficients for these measures were 0.74, 0.88, and 0.77, respectively.
LV Remodeling

LV remodeling was assessed by CMR 93 (89–97) days post-revascularization. LV ejection fraction at follow-up was 57% (34% to 67%). Positive remodeling was seen in the ventricular volumes, with the end-diastolic volume decreasing from 129 mL (106–149 mL) to 103 mL (90–128 mL; \( P = 0.02 \)). End-systolic volume similarly reduced from 58 mL (46–81 mL) to 47 mL (36–57 mL; \( P = 0.04 \)). There was a trend to a reduced volume of hyperenhancement at follow-up, in terms of absolute infarct mass (7.6 g [2.6–11.2 g] versus 6.2 g [2.1–10.3 g]; \( P = 0.06 \)) and relative to overall LV mass (7.1% [2.6–11.3%] versus 6.0% [2.3–11.1%]; \( P = 0.08 \)). At baseline, median regional %WT in the infarct territory was 48% (27% to 52%) improving to 70% (43% to 84%; \( P < 0.0001 \)), post-revascularization, with a median improvement of 23% (4% to 36%; Table 2).

The microcirculation-derived diastolic BEW was strongly predictive of both initial baseline wall thickening (\( R = 0.83; P < 0.0001 \)) and the eventual change in regional wall thickening (%WT) (\( R = 0.68; P = 0.001 \); Figure 3B), as was the distally originating systolic BCW (\( R = 0.62; P = 0.002 \), and \( R = 0.52, P = 0.02 \), respectively). There was a statistically nonsignificant association between baseline and improvement in %WT with respect to the aorta-derived systolic FCW (\( R = 0.44, P = 0.07 \), and \( R = 0.48, P = 0.06 \), respectively). In addition, there was an inverse relationship between IRA hMR and baseline wall thickening (\( R = –0.52; P = 0.02 \)), although this was not statistically significant when associated with regional recovery function (\( R = –0.34, P = 0.07 \)).

By receiver-operator characteristic analysis, a BEW value \( > 2.81 \text{W m}^{-2} \text{s}^{-2} \times 10^5 \) provided the highest sensitivity (0.91) and specificity (0.82) for predicting recovery of regional function (%WT) in this cohort, with an accuracy (area under the curve) of 0.88. Similarly, an hMR value of \( \leq 2.41 \text{mm Hg cm}^{-1} \text{s} \) predicted functional recovery with a sensitivity, specificity, and area under the curve of 0.82, 0.64, and 0.68, respectively (Figure 4). The Delong receiver-operator characteristic comparison test confirmed the superior predictive accuracy of

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>30% Recovery in WT</th>
<th>30% Recovery in WT</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of completed protocols</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>57 (51–67)</td>
<td>56 (47–71)</td>
<td>58 (52–79)</td>
<td>0.27</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (82)</td>
<td>10 (82)</td>
<td>8 (73)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (45)</td>
<td>5 (45)</td>
<td>5 (45)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (14)</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>15 (68)</td>
<td>8 (73)</td>
<td>7 (64)</td>
<td>0.66</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>8 (36)</td>
<td>2 (18)</td>
<td>6 (55)</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI, kg/m², median (IQR)</td>
<td>26 (25–28)</td>
<td>26 (21–31)</td>
<td>27 (23–32)</td>
<td>0.64</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type of ACS</td>
<td></td>
<td></td>
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<td>NSTEMI, n (%)</td>
<td>22 (100)</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration from symptom onset to CMR, median h (IQR)</td>
<td>46 (43–76)</td>
<td>45 (39–164)</td>
<td>47 (44–172)</td>
<td>0.09</td>
</tr>
<tr>
<td>Duration from symptom onset to angiogram, median h (IQR)</td>
<td>48 (48–78)</td>
<td>45 (45–72)</td>
<td>50 (46–210)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Troponin T, µg/L, median (IQR)</td>
<td>1.35 (0.40–1.21)</td>
<td>0.89 (0.22–1.59)</td>
<td>1.63 (0.61–4.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/Cx/RCA, n</td>
<td>14/3/5</td>
<td>6/4/1</td>
<td>7/3/1</td>
<td>n/a</td>
</tr>
<tr>
<td>Pre-PCI QCA, median % (IQR)</td>
<td>78 (71–88)</td>
<td>77 (70–85)</td>
<td>78 (72–87)</td>
<td>0.11</td>
</tr>
<tr>
<td>Post-PCI FFR, median (IQR)</td>
<td>0.94 (0.91–0.98)</td>
<td>0.93 (0.91–0.95)</td>
<td>0.94 (0.92–0.97)</td>
<td>0.25</td>
</tr>
<tr>
<td>Medications (on discharge), n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>22 (100)</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>22 (100)</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>21 (95)</td>
<td>10 (91)</td>
<td>11 (100)</td>
<td>0.95</td>
</tr>
<tr>
<td>ACE inhibitor (or ARB)</td>
<td>22 (100)</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Statin</td>
<td>22 (100)</td>
<td>11 (100)</td>
<td>11 (100)</td>
<td>1.0</td>
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<tr>
<td>Calcium antagonist</td>
<td>6 (27)</td>
<td>4 (36)</td>
<td>2 (18)</td>
<td>0.16</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>4 (18)</td>
<td>2 (18)</td>
<td>2 (18)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, Acetyl-salicylic acid; BMI, body mass index; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; IQR, interquartile range; LAD/Cx/RCA, left anterior descending/circumflex/right coronary artery; MI, myocardial Infarction; NA, not applicable; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; and QCA, quantitative coronary angiography.
**Table 2. Cardiac CMR Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Index Presentation</th>
<th>Follow-up</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of completed protocols</td>
<td>22</td>
<td>22</td>
<td>NA</td>
</tr>
<tr>
<td>Time of MRI following symptom onset (d), median (IQR)</td>
<td>2 (2–3)</td>
<td>93 (89–97)</td>
<td>NA</td>
</tr>
<tr>
<td>Volumetric analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL, median (IQR)</td>
<td>129 (106–149)</td>
<td>103 (90–128)</td>
<td>0.02</td>
</tr>
<tr>
<td>LVESV, mL, median (IQR)</td>
<td>58 (46–81)</td>
<td>47 (36–57)</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEF, %, median (IQR)</td>
<td>56 (31–68)</td>
<td>57 (34–67)</td>
<td>0.55</td>
</tr>
<tr>
<td>Quantitative infarct size characterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct mass, g, median (IQR)</td>
<td>7.6 (2.6–11.2)</td>
<td>6.2 (2.1–10.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Infarct mass % of left ventricular mass, median (IQR)</td>
<td>7.1 (2.6–11.3)</td>
<td>6.0 (2.3–11.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Quantitative regional wall analysis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Wall thickening, %, median (IQR)</td>
<td>48 (27–52)</td>
<td>70 (43–84)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Improvement in wall thickening %, median (IQR)</td>
<td>-</td>
<td>23 (4–36)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance; IQR, interquartile range; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; and LVEF, left ventricular ejection fraction.

**Discussion**

Our study indicates that the magnitude of the backward expansion wave energy in the IRA is strongly predictive of myocardial recovery after an NSTEMI, highlighting its potential use as an index of myocardial viability that can be obtained during cardiac catheterization. Furthermore, we have demonstrated that the BEW is reduced after ACS, in proportion to the magnitude of infarction.

**Phasic WIA Versus Means-per-Beat Assessment of Microvascular Function**

The ability to prospectively risk stratify patients after myocardial infarction is paramount to the optimization of outcome. The severity of microvascular dysfunction postinfarction has been demonstrated to be an important correlate of LV functional recovery, cardiovascular morbidity, and mortality and is proportionate to infarct size. Coronary flow reserve and fractional flow reserve after acute myocardial infarction have both been found to be predictive of myocardial recovery, albeit with variable accuracy. However, supportive evidence correlating fractional flow reserve with viability is limited in the acute setting, when microvascular derangement is at its peak, potentially affecting the accuracy of fractional flow reserve in this context. The dependence of coronary flow reserve on prevailing hemodynamic conditions and epicardial coronary disease has also limited its applicability. Consequently, both measures have been largely superseded by more specific indices of microvascular resistance, which have been more consistently associated with myocardial viability. Fearon et al first demonstrated the use of the index of microvascular resistance in evaluating the microcirculation, confirming that it was an independent predictor of infarct size and LV recovery after STEMI. These findings have subsequently been reproduced by several investigators who have assessed the index of microvascular resistance after successful primary PCI. Similarly, Kitabata et al demonstrated that the Doppler-based index hMR is predictive of infarct size and recovery in function after reperfusion of STEMI. However, it should be noted that these indices have previously only been evaluated in the setting of acute STEMI. To our knowledge, the current study is the first reported evaluation of hMR as a measure of myocardial recovery after NSTEMI. Our findings suggest that the correlation between hMR and either infarct size

**Figure 3.** Backward expansion wave (BEW) vs infarction and wall thickening parameters.
A. Infarct-related artery (IRA) BEW vs absolute late-gadolinium enhancement (LGE) mass.
B. Regional improvement in wall-thickening vs IRA BEW.
or the likelihood of recovery of regional function may not be as strong as it is after STEMI. Although this difference may relate to the smaller extent of infarction in our NSTEMI population compared with the previous STEMI studies, it is possible that microvascular resistance alone may not be an adequate measure of myocardial viability in NSTEMI.

The use of wave energetics to analyze phasic coronary pressure and flow represents a paradigm shift in evaluating microvascular function and has the potential to provide more detailed insights into the determinants of myocardial perfusion than the traditional means-per-beat methods. This may explain the superior diagnostic accuracy of the BEW, which interrogates microvascular function and regional contractility, the codeterminants of myocardial viability.

Diastolic Wave Energy: The Backward Expansion Wave

The myocardial-microvascular interaction is pivotal in governing coronary pulsatile flow and transmural myocardial flow distribution. Although aortic pressure is the main determinant of coronary arterial pressure and flow, the relationship is complex and nonlinear, with various models alluding to the impedence of systolic coronary flow by the contraction of the myocardium surrounding the intramyocardial microcirculation. The BEW is the dominating microcirculatory wave energy that propagates coronary flow and, therefore, myocardial perfusion during diastole. The BEW occurs as a result of diastolic relaxation of the microvasculature, creating a suction effect, subsequently accelerating flow within the microvascular bed. It can therefore be considered an integrated measure of the myocardial-microvascular interaction. The effect of varying microvascular resistance on this wave, with both pharmacological vasodilation and enhanced LV lusitropy, results in a decreased compressive force on the microcirculation, thereby increasing the magnitude of the BEW. Davies et al demonstrated a 30% reduction in the magnitude of the BEW in patients with hypertension-related LV hypertrophy, a population known to have globally impaired microvascular function and LV lusitropy, when compared with a group of matched controls.

Myocardial ischemia and infarction affect both aspects of the myocardial-microvascular interaction, namely, contractility and microvascular function, making the BEW wave an attractive tool for evaluating this relationship. The reduction in BEW amplitude after infarction found in our study of NSTEMI mirrors the previous observations of the impact of infarction on diastolic coronary flow in the setting of STEMI. Iwakura et al demonstrated the aberrant nature of diastolic flow after infarction, observing a disproportionate attenuation of diastolic flow velocity deceleration compared with systolic flow. In our study, the spatial heterogeneity of contractility and microvascular function after infarction is reflected in the differences between IRA and remote vessel wave energies (Figure 1). BEW magnitude was significantly reduced, by 26%, in the infarct region compared with the noninfarct zone (Table 3). Furthermore, the IRA BEW magnitude was predictive of regional LV recovery, whereas the reference BEW, remote from the infarct zone, was not related to the likelihood of recovery.

Systolic Wave Energies: Backward and Forward Compression Waves

The forward compression wave energy occurs at the onset of systole and is an accelerating energy driven from the aortic end of the circulation, primarily resulting from the pressure.
transmitted by ventricular contraction. Sun et al,40 examined this association in an animal model, using WIA to measure the effect of pacing-induced perturbations in LV function to show that increasing LV contraction increased the ventricular driving force, coronary pressure, and subsequently the magnitude of FCW. We have demonstrated for the first time in patients that alterations of LV ejection directly relate to the resultant FCW energy, with those with a low LV ejection fraction having a reduced FCW energy. Furthermore, the weaker association of FCW with infarct size compared with BEW or BCW may reflect the fact that its primary determinant, LV ejection fraction, is a global measure of systolic function, which is affected by diminished contractility in the infarct zone, as well as compensatory hypercontractility in the remote zones.

The BCW is the other significant wave in systole. It is decelerating in nature and arises from the compressive force on the microcirculation during systole, with the net difference between FCW and BCW determining flow during systole. The linear relationship observed with LV ejection fraction confirms that BCW is governed by the extrinsic compression exerted by the myocardium on the microvasculature. Because BCW represents regional systolic contractility, it is also a predictor of infarct size, although to a lesser extent than the diastolic BEW. The relative amplitudes of FCW and BCW thus reflect the opposing effects of LV contraction on coronary perfusion pressure and compression of the microcirculation during systole.

Limitations
This was a small, single-center study but is the first human study to examine the relationship and effects of recent myocardial infarction on coronary wave intensity. Despite being a cross-sectional study, patients with previous myocardial infarction and those with CMR signs suggestive of non-ischemic myocardial disease or valvular heart disease were excluded to minimize confounders. Furthermore, we have used a sum-of-squares method to derive coronary wave speed, which in turn was used to separate wave energies.23 This technique has been validated in subjects with normal coronary arteries, and its applicability in the setting of ACS and obstructive epicardial disease is unknown.

The results presented above are based on coronary pressure and Doppler measurements taken after PCI, although the eventual use of this technique in clinical practice may be as a parameter measured before PCI to guide the selection of patients for revascularization. We did obtain pre-PCI measurements in a subset (n=11) of the overall cohort, which demonstrates that it is feasible and safe to assess BEW before PCI and, furthermore, that there is a close correlation between BEW derived from measurements taken before and after PCI (r=0.70, P=0.01; where BEW<sub>pre</sub>=0.68×BEW<sub>post</sub>+1.2 W m<sup>–2</sup> s<sup>–2×10<sup>5</sup></sup>). Additionally, although the data presented here were obtained at a center with considerable interventional experience in intracoronary hemodynamic assessment techniques with specific relevance to use of the dual-sensor pressure-flow wire, we think that this technology remains a reproducible method of invasively interrogating the coronary circulation, which could be adopted more widely in the interventional community. Also, as a consequence of the small sample size and the use of unadjusted statistical tests adopted within the study, there is potential for a type 1 error affecting the results. Therefore, further investigation is warranted to confirm these initial findings. Finally, the eventual infarct size in this NSTEMI population was relatively modest. However, the use of BEW for predicting viability is expected to be even better with larger infarctions, but this requires prospective validation.

Conclusions
Microcirculatory expansion wave energy is a new index that, in this homogenous ACS cohort, has been shown to specifically and quantitatively assess the magnitude and location of infarction and may allow the prediction of late myocardial recovery after ACS. Coronary WIA may provide an accurate adjunctive method of assessing myocardial viability during cardiac catheterization after ACS.

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Disclosures
None.
References


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