Estimation of coronary wave intensity analysis using noninvasive techniques and its application to exercise physiology

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Broyd CJ, Nijjer S, Sen S, Petracco R, Jones S, Al-Lamee R, Foin N, Al-Bustami M, Sethi A, Kaprielian R, Ramrakha P, Khan M, Malik IS, Francis DP, Parker K, Hughes AD, Mikhail GW, Mayet J, Davies JE. Estimation of coronary wave intensity analysis using noninvasive techniques and its application to exercise physiology. Am J Physiol Heart Circ Physiol 310: H619–H627, 2016. First published December 18, 2015; doi:10.1152/ajpheart.00575.2015.—Wave intensity analysis (WIA) has found particular applicability in the coronary circulation where it can quantify traveling waves that accelerate and decelerate blood flow. The most important wave for the regulation of flow is the backward-traveling decompression wave (BDW). Coronary WIA has hitherto always been calculated from invasive measures of pressure and flow. However, recently it has become feasible to obtain estimates of these waveforms noninvasively. In this study we set out to assess the agreement between invasive and noninvasive coronary WIA at rest and measure the effect of exercise. Twenty-two patients (mean age 60) with unobstructed coronary arteries underwent invasive WIA in the left anterior descending artery (LAD). Immediately afterwards, noninvasive LAD flow and pressure were recorded and WIA calculated from pulsed-wave Doppler coronary flow velocity and central blood pressure waveforms measured using a cuff-based technique. Nine of these patients underwent noninvasive coronary WIA assessment during exercise. A pattern of six waves were observed in both modalities. The BDW was similar between invasive and noninvasive measures [peak: 14.9 ± 7.8 vs. −13.8 ± 7.1 × 103 W·m⁻²·s⁻², concordance correlation coefficient (CCC): 0.73, P < 0.01; cumulative: −64.4 ± 32.8 vs. −59.4 ± 34.2 × 103 W·m⁻²·s⁻³, CCC: 0.66, P < 0.01], but smaller waves were underestimated noninvasively. Increased left ventricular mass correlated with a decreased noninvasive BDW fraction (r = −0.48, P = 0.02). Exercise increased the BDW; at maximum exercise peak BDW was −47.0 ± 29.5 × 103 W·m⁻²·s⁻² (P < 0.01 vs. rest) and cumulative BDW −19.2 ± 12.6 × 103 W·m⁻²·s⁻³ (P < 0.01 vs. rest). The BDW can be measured noninvasively with acceptable reliably potentially simplifying assessments and increasing the applicability of coronary WIA.

Coronary wave-intensity analysis can be measured noninvasively potentially translating it from a primary research tool to a clinical modality. Application to larger studies will permit exploration of its potential predictor of outcome and facilitate examination of the effect of pharmacological (or other) interventions on coronary wave intensity in various subgroups.

Wave intensity analysis (WIA) provides a time-domain separation of up- and downstream wavefronts travelling at a single point within a fluid medium and can elucidate the basis of temporal blood flow velocity changes within the cardiovascular system. As the product of the first derivatives of pressure (dP) and flow (dU), it is able to both qualify (in terms of direction) as well as quantify (in terms of magnitude) energy transfer.

In humans it has been applied to many large arteries including the carotid and radial arteries (26, 43) as well as the aorta (17) but has proven most useful in investigating the coronary circulation where pressure gradients arising both proximally (aortic) and distally (myocardial) influence coronary flow (7). The dominant wave driving coronary flow, the backward decompression wave, originates distally from the myocardium at the onset of diastole and is generated by active myocardial relaxation and resultant decompression of the intramyocardial microvasculature producing a distal-to-proximal pressure gradient and thus a “suction” effect. The backward decompression wave is reduced in left ventricular hypertrophy (7), is increased in severe aortic stenosis (5), is increased in response to pacing (40) or exercise (23), and can be used to predict myocardial recovery after infarction (39).

While many peripheral arteries are amenable to interrogation using noninvasive Doppler and tonometric-based surrogates of pressure, until now the only way to perform coronary WIA is invasively during angiography using intracoronary pressure- and flow-sensor–tipped wires. However, now it is possible to obtain acceptable surrogates of these measures noninvasively using transthoracic Doppler ultrasound (34) and tonometry or cuff-based estimates of the central (aortic) pressure waveform (16, 22, 24).

Therefore, we set out to perform a noninvasive measurement of coronary WIA using these modalities in patients with normal coronary arteries. For further validation we assessed the association of the magnitude of the backward decompression wave with two parameters that are known to affect wave intensity: exercise and left ventricular mass.

METHODS

Subjects. Twenty-eight consecutive subjects were recruited from patients scheduled for coronary angiography with typical or atypical chest pain and a positive functional test. Exclusion criteria included known ischemic heart disease, valvular pathology, evidence of regional wall motion abnormalities, and renal impairment (creatinine >120 μmol/l). The study was approved by the Fulham-Local Re-
CONSTRUCTION OF NONINVASIVE CORONARY WIA

Invasive pressure and flow measurements. Cardiac catheterization was performed via either the femoral or radial approach. After diagnostic angiography, studies were closely inspected by two operators and only patients with angiographically normal arteries proceeded to have hemodynamic measures recorded. All patients received intravenous heparin (5,000 units) before insertion of the intracoronary pressure-flow wire. No other drugs were administered during the procedure. A guide catheter was used to intubate the left coronary system, and a 0.014-in. diameter combined pressure- and flow-tipped wire (Combowire; Volcano Therapeutics) was passed into the mid-LAD and manipulated until an optimal flow and pressure signal were obtained. Pressure and flow data were recorded using a Combomap console (Volcano Therapeutics) over a period of 1 min.

Noninvasive pressure and flow measurements. Immediately following completion of angiography and exit from the coronary catheter laboratory, noninvasive coronary flow and pressure waveforms were obtained. Echocardiography was performed using either a Phillips iE33 (Amsterdam, The Netherlands) or Esaote MyLabTwice (Genova, Italy). The LAD was imaged initially in the parasternal long-axis view with high-wall filters, low-pulse Doppler filters and a color pulse repetition frequency typically in the range of 15–25 cm/s, settings essential for this technique (34). With the septum maintained centrally the probe was rotated clockwise and moved laterally across the chest wall until the LAD was clearly in view with an angulation of <20° to the probe. Pulse-wave Doppler was applied with a sampling width of 7.5–10 mm, and multiple coronary flow signals were recorded. Data were exported as a high-resolution image file. Simultaneously, a suprasystolic waveform was recorded and calibrated with the brachial blood pressure using a cuff-based device (Pulsecor, Auckland, New Zealand). The unprocessed data were exported as a Matlab file. A full echocardiographic study was then undertaken including calculation of left ventricular mass (19).

Data processing. The central pressure waveform was estimated from the Pulsecor raw data using a modification of the approach described by Lowe et al. (24). A minimum of two suprasystolic recordings were made; anything less than “good” quality data (as recognized by the Pulsecor system’s quality control) was repeated. Each waveform was then aligned according to the peak negative dp/dr before ensemble averaging to prevent oversmoothing of the early diastolic section of the pressure waveform, which is essential for the construction of the backward decompression waveform.

Noninvasive pressure and flow data were aligned using the “foot” of the pressure waveform and the ECG-QRS from echocardiography (mean number of cardiac cycles: 21 ± 9). Invasive data were aligned according to echocardiography gating accounting for the inherent Combomap flow-pressure offset (mean number of cardiac cycles: 63 ± 58).

After alignment and beat selection, both invasive and noninvasive data were processed using the same automated Matlab software, which involved an identical Savitsky-Golay filter (polynomial order 3, window size 51). The noninvasive data were analyzed by an observer blinded to the invasive analysis results.

Wave-intensity analysis. Wavespeed (c) was calculated using the single-point method (8). WIA was calculated as previously described (7). Briefly, we used the product of the first time derivatives of pressure (dp/dr) and velocity (dU/dr) so the results are independent of the sampling frequency used. The waves can be separated into proximally (WI+) and distally (WI−) originating waves as well as net wave intensity using:

\[
WI_{NET} = WI_{+} - WI_{-} = \frac{dP}{dr} \left[ \frac{dP}{dr} + \frac{dU}{dr} \right] \]

where \( \rho \) is the density of blood (taken as 1,050 kg/m³).

To separate coincident waves from proximal and distal origins the change in pressure was separated into its wave components: \( dP_{+/dr} \) (proximal) and \( dP_{−/dr} \) (distal).

\[
\frac{dP_+}{dr} = \frac{1}{2} \left( \frac{dP}{dr} + \rho c \frac{dU}{dr} \right)
\]

\[
\frac{dP_-}{dr} = \frac{1}{2} \left( \frac{dP}{dr} - \rho c \frac{dU}{dr} \right)
\]

Cumulative wave intensity (i.e., wave energy) was calculated for each wave by measuring the area under the peak of the wave intensity vs. time curve. The cumulative intensity of each individual wave was also calculated as a proportion of the total cumulative wave intensity over the cardiac cycle (termed “wave energy fraction”).

Noninvasive coronary wave intensity analysis in exercise. A subgroup of 10 patients went on to have noninvasive coronary wave intensity calculated during exercise. Patients were selected on the basis of optimal coronary flow windows and the physical ability to perform an exercise regimen reliably. They were asked to withhold any rate-limiting pharmacological agents in the 48 h before attendance and avoid alcohol, nicotine, or nitrates in the preceding 24 h.

Patients were exercised during echocardiography using a semirecumbent ergometer exercise bike (Ergoline, Stuttgart, Germany). Patients were positioned according to their optimal echocardiographic windows, typically semirecumbent at 45° and towards their left lateral side. Coronary flow and central aortic pressure were recorded during graded exercise according to a predetermined standardized incremental exercise protocol (32) based on the patient’s weight and age, typically starting at 25 W and increasing by 20 W each minute. Data were acquired when the heart rate was 20 and 40 beats/min above resting following cessation of exercise. To preserve an optimal pressure signal, an assistant held the patients arm static following exercise while Pulsecor data were simultaneously acquired.

Reproducibility. For each patient, hemodynamic data were recorded before and after the conventional echocardiographic study. The reproducibility of hemodynamic measurements was calculated by examining separate 30-s noninvasive recordings of blood pressure, velocity, and wave intensity for each patient.

Statistics. The data were analyzed using STATA 11 and Matlab R2015a. Continuous variables are reported as mean ± SD. The Bland-Altman method was used to quantify agreement between noninvasive and invasive wave intensity and to analyze reproducibility data. Lin’s correlation coefficient was used to express concordance (CCC), and the coefficient of variation (CV) was calculated for reproducibility data as the ratio of the SD of difference between measures to the mean value of the measure. Two-dimensional cross-correlation coefficients were used as a measure of similarity between noninvasive and invasive waveforms. Invasive and noninvasive values were compared using a Wilcoxon matched-pairs signed-ranks test. Exercise hemodynamic data were analyzed using Cuzick’s test for trend. Correlation was assessed with Pearson’s correlation coefficient. Fisher’s r-to-z transformation was used to compare correlation coefficients. \( P < 0.05 \) was deemed significant.

RESULTS

Patient characteristics. Of the 28 patients recruited, 23 had appropriate echocardiographic windows to allow coronary flow analysis. In one patient it was impossible to obtain an adequate invasive Doppler signal for analysis. The remaining 22 patients make up the study population. Mean age was 60 ± 12 yr (14 male). Systolic function was preserved (mean ejection fraction: 0.56 ± 0.08).
undergoing combined invasive and noninvasive LAD wave-dance (CCC 0.73, P < 0.01). Mean resting Pa/Pd was 305 ms invasively and 281 ms noninvasively (r = 0.99 ± 0.01). The time of minimum dP/dt was higher invasively than noninvasively (−0.57 ± 0.21 vs. −0.36 ± 0.16 mmHg/s; P < 0.01) but with a favorable concordance (CCC = 0.44, P < 0.01); additionally, the mean cross-correlation coefficient between invasive and noninvasive pressure waveforms was very high (r = 0.99 ± 0.01). The time of minimum dP/dt from the foot of the systolic aortic upstroke was 305 ms invasively and 281 ms noninvasively (P = 0.02).

As previously described, six different waves were identified in the cardiac cycle. Each wave was characterized by origin and direction of travel (forward-traveling waves originating proximally and backward-traveling waves originating distally), character (compression or decompression), and effect on coronary blood flow velocity (acceleration or deceleration waves) (7). Focus was given to the forward compression wave, forward decompression wave, and backward decompression wave as the waves of most physiological importance (Fig. 1).

Peak backward decompression wave was −14.9 ± 7.8 × 10^4 W·m^{-2}·s^{-2} invasively and −13.8 ± 7.1 × 10^4 W·m^{-2}·s^{-2} noninvasively and measures showed good concordance (CCC 0.73, P < 0.01). Cumulative wave intensity was −64.4 ± 32.8 × 10^2 W·m^{-2}·s^{-1} invasively compared with −59.4 ± 34.2 × 10^2 W·m^{-2}·s^{-1} noninvasively (CCC: 0.66, P < 0.01; Fig. 2 and Table 3).

The noninvasive measures of other waves underestimated their magnitude compared with invasive measures (Table 3).

Table 1. Baseline patient demographics of 22 patients undergoing combined invasive and noninvasive LAD wave-intensity analysis

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Male, %</td>
<td>14 (64)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 ± 12</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.5 ± 17</td>
</tr>
<tr>
<td>BMI, kg/m^2</td>
<td>29.1 ± 3.9</td>
</tr>
<tr>
<td>Hypertensive, %</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Cholesterol therapy, %</td>
<td>12 (55)</td>
</tr>
<tr>
<td>DM, %</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pharmacological therapy</td>
<td></td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>3 (14)</td>
</tr>
<tr>
<td>ACE inhibitor/angiotensin receptor blocker, %</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Calcium channel antagonist, %</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Thiazide diuretic, %</td>
<td>2 (9)</td>
</tr>
<tr>
<td>α-Blocker, %</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Statin, %</td>
<td>12 (55)</td>
</tr>
</tbody>
</table>

Values are mean ± SE. LAD, left anterior descending artery; BMI, body mass index; DM, diabetes mellitus.

This meant the fraction backward decompression wave intensity was higher in the noninvasive group (29.7 ± 9.5% noninvasively vs. 22.1 ± 5.4% invasively, P < 0.01) but there was a correlation between the two techniques (r = 0.45, P = 0.04). Wave speed was also lower by noninvasive methods (Table 3).

As previously reported (4), a correlation was also seen between the noninvasive forward compression wave and the backward decompression wave (r = −0.44, P = 0.04); this was almost identical to that seen invasively (r = −0.44, P = 0.04; Fisher’s z = 0, P > 0.99).

Reproducibility. The mean ± SD of the difference between the separate 30-s recordings of blood pressure was 2.2 ± 2.0 mmHg (CV = 2.4%). The mean ± SD of the difference between the separate 30-s recordings of flow velocity was 0.7 ± 0.7 cm/s (CV = 2.0%). The mean ± SD of the difference between the separate 30-s recordings of the cumulative backward decompression wave was −1.6 ± 2.3 ± 10^2 W·m^{-2}·s^{-1} (CV = 2.0%). The mean ± SD of the difference between the separate 30-s recordings of the peak backward decompression wave was −0.8 ± 0.8 ± 10^4 W·m^{-2}·s^{-2} (CV = 4.4%).

Left ventricular mass. Mean left ventricular mass was 163 ± 37 g with five patients meeting the definition of left ventricular hypertrophy (19). There was a significant negative correlation between left ventricular mass and both noninvasive (r = −0.48, P = 0.02; Fig. 3) and invasive (r = −0.49, P = 0.01) backward decompression wave fraction. No significant difference was found between the two correlation coefficients (z = 0.21, P = 0.83). There was also a significant positive correlation between left ventricular mass in the noninvasive forward compression wave fraction (r = 0.50, P = 0.02). No other correlations were noted between mass and any of the other waves or their fractional energy.

Exercise wave intensity. One patient was excluded from this subanalysis because of technically inadequate coronary flow sampling during exertion. Peak coronary flow rose during exercise from 23.2 ± 8.2 to 42.2 ± 17.8 cm/s (P < 0.01 for trend) as did systolic pressure (120 ± 13.0 to 140 ± 23.4

Table 2. Baseline echocardiographic data of 22 patients undergoing combined echocardiographic and noninvasive LAD wave-intensity analysis

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Dimensional measurements, cm</td>
<td></td>
</tr>
<tr>
<td>LVEDd</td>
<td>4.5 ± 0.5</td>
</tr>
<tr>
<td>LVEDs</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>IVSd</td>
<td>1.04 ± 0.21</td>
</tr>
<tr>
<td>PWd</td>
<td>1.02 ± 0.21</td>
</tr>
<tr>
<td>IVSs</td>
<td>1.6 ± 0.43</td>
</tr>
<tr>
<td>PWs</td>
<td>1.7 ± 0.43</td>
</tr>
<tr>
<td>Mitral inflow, cm/s</td>
<td>E 65.5 ± 16</td>
</tr>
<tr>
<td></td>
<td>A 68.5 ± 17</td>
</tr>
<tr>
<td>Mean tissue Doppler, cm/s</td>
<td>E' 9.4 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>s' 8.7 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>E/A 0.96 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>E/e' 7.0 ± 2.9</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>163 ± 37</td>
</tr>
</tbody>
</table>

Values are mean ± SD. LVEDd and LVEDs, left ventricular end-developed diastole and systole pressure; IVSd and IVSs, interventricular septum diastole and systole pressure; PWd and PWs, pulse-wave diastole and systole; LV, left ventricle; E/A, early and late velocities.
mmHg, \( P = 0.07 \) for trend). Diastolic pressure rose only modestly from 82.3 ± 10.5 to 85.9 ± 11.0 mmHg (\( P = 0.68 \) for trend).

Both peak and cumulative backward decompression wave intensity analyses demonstrated a progressive increase with exercise. Peak was \(-9.7 \pm 6.3 \times 10^4\) W·m\(^{-2}\)·s\(^{-2}\) at baseline and increased to \(-12.5 \pm 6.3 \times 10^4\) W·m\(^{-2}\)·s\(^{-2}\) at moderate exercise and \(-47.0 \pm 29.5 \times 10^4\) W·m\(^{-2}\)·s\(^{-2}\) at peak (\( z = -3.33, P < 0.01 \) for trend). Cumulative was \(-4.3 \pm 3.2 \times 10^3\) W·m\(^{-2}\)·s\(^{-1}\) at rest and rose to \(-6.6 \pm 3.3 \times 10^3\) W·m\(^{-2}\)·s\(^{-1}\) at moderate exercise and \(-19.2 \pm 12.6 \times 10^3\) W·m\(^{-2}\)·s\(^{-1}\) at peak (\( z = -3.80, P < 0.01 \) for trend; Figs. 4 and 5 and Table 4).

**DISCUSSION**

We have demonstrated that the coronary wave intensity profile can be measured with reasonable fidelity noninvasively using Doppler echocardiography and the central blood pressure waveform estimated from a brachial blood pressure cuff device. The agreement between wave intensity measured invasively and noninvasively was good, the correlation between the backward decompression wave and left ventricular mass was similar between invasive and noninvasive methods, and exercise induced a graded increase in the backward decompression wave intensity demonstrating

![Fig. 1. Invasive vs. noninvasive wave intensity analysis. Six waves were identified through both modalities. The 3 most clinically relevant waves are identified: 1) the forward compression wave in early systole generated from ventricular contraction with an open aortic valve, 2) the forward decompression wave created from the slowing of ventricular contraction at the end of systole, and 3) the backward decompression wave generated by the reexpansion of the intramyocardial vessels that were compressed during systole. While the other waves of the cardiac cycle are underestimated noninvasively, a good concordance is seen with backward decompression wave.](http://ajpheart.physiology.org/content/early/2017/09/20/ajpheart.00575.2015.full-113626-00575F1){/fig}

**Table 3. Invasive vs. noninvasive coronary hemodynamics**

<table>
<thead>
<tr>
<th>Wave intensity</th>
<th>Noninvasive</th>
<th>Invasive</th>
<th>Difference</th>
<th>CCC*</th>
<th>( P )†</th>
<th>( P )‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak velocity</td>
<td>29.2 ± 6.5</td>
<td>29.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.49</td>
<td>&lt;0.01</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean velocity</td>
<td>17.5 ± 4.3</td>
<td>17.2 ± 6.7</td>
<td>0.3 ± 0.6</td>
<td>0.42</td>
<td>&lt;0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>Minimum velocity</td>
<td>11.3 ± 3.1</td>
<td>7.45 ± 4.1</td>
<td>3.9 ± 0.5</td>
<td>0.15</td>
<td>0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>Central pressure, mmHg</td>
<td>122 ± 16.2</td>
<td>127 ± 21.2</td>
<td>5.0 ± 7.7</td>
<td>0.45</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic mmHg</td>
<td>77.4 ± 9.4</td>
<td>75.2 ± 9.4</td>
<td>2.2 ± 2.3</td>
<td>0.65</td>
<td>&lt;0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean mmHg</td>
<td>91.1 ± 10.6</td>
<td>92.2 ± 12.1</td>
<td>1.1 ± 1.0</td>
<td>0.37</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. °Lin’s concordance correlation coefficient (CCC) and †P value for the significance of this value. ‡P values for direct comparison are also displayed.*
the sensitivity of this noninvasive method to a physiological intervention.

*Noninvasive measures of flow, pressure, and wave intensity.* With the introduction of newer echocardiography machines with second harmonic imaging and high-frequency transducers, it has become possible to obtain a very accurate coronary flow envelope that shows equivalence with invasively derived measures (14, 34, 35). This technique is now able to calculate coronary flow reserve (CFR) and has been used to predict outcome in a variety of disease states (2, 3, 33).

Previous work has sought to use single, resting measures of coronary flow alone to assess microvascular dysfunction with varying degrees of success. To that end, correlates have been recognized among invasively measured systolic flow reversal (41), diastolic deceleration time (15, 20), and recovery after myocardial infarction and these markers have been adopted noninvasively as well (29). Combining noninvasive pressure and flow data to calculate coronary wave intensity offers a potentially valuable index of coronary hemodynamics.

The derivation of wave intensity from pressure and flow tracings has previously been successfully performed noninvasively in carotid (1, 28), brachial, and radial arteries (43). This has resulted in a large increase in its applicability providing insights into its relationship to outcomes (25) and the differential effect of therapies (26). We have now shown that is also possible to measure wave intensity in the LAD using noninvasive measures of central pressure and coronary flow. With this approach the backward decompression wave is equivalent to that seen in previous invasive studies (7).

Our approach was focused on the three most clinically relevant waves within the cardiovascular system, particularly the backward decompression wave as this provides insights regarding the microcirculatory drive to coronary flow (5, 7, 11, 18). This wave has the largest magnitude and therefore least potential for signal-to-noise errors. Additionally, we used the peak negative dP/dt of the pressure waveform for alignment before ensembling and optimized the Doppler envelope for this portion of the cardiac cycle. These factors may explain firstly why our measure of the backward decompression wave was most accurate but also, in part, why the other waves were underestimated since coregistration errors in the ensemble will tend to increase with distance from the fiducial point. Nevertheless, a strong correlation between the forward compression wave and backward decompression wave was seen as has been recognized invasively (7) implying an adequate approximation over the whole cycle.

To test the validity of our measure of the backward decompression wave further, we examined it under variable physiological and pathological environments and assessed whether it performed similarly to reported invasive measures.

*Left ventricular mass.* Increased left ventricular mass is associated with adverse cardiovascular outcomes (12, 21). CFR is reduced with left ventricular hypertrophy (13), a feature that is reversible with therapy (27) so that despite an increased muscle mass, the ability of the heart to regulate its own blood flow...
supply is attenuated in left ventricular hypertrophy, which reflects an inefficiency of myocardial function.

WIA can also provide an insight into this myocardial efficiency and can demonstrate the interplay between myocardial structure and coronary flow despite similar coronary flow velocity rates (42). Invasive studies have shown that left ventricular hypertrophy results in a reduction in the backward decompression wave energy fraction (7). As such, coronary wave intensity may be able to provide prognostic information in a similar fashion to CFR and a technique, such as this one, to increase its potential applicability would therefore be useful.

In the present study we have confirmed the relationship between invasively assessed backward decompression wave energy fraction and left ventricular mass and gone on to show this relationship is detected using our noninvasive method for measuring coronary wave intensity with acceptable accuracy.

While only five patients from our cohort met a definition of left ventricular hypertrophy, the effect of left ventricular mass on both coronary physiology (27) and mortality (12) is continuous as is WIA. We would therefore anticipate a correlation between left ventricular mass and wave intensity even when left ventricular mass is within the “normal” range and this is indeed what we found.

Exercise physiology. At rest, hemoglobin concentration and oxygen extraction of coronary flow are already at 70–80% maximum capacity, and therefore, the resultant fivefold increase in the oxygen requirements of the myocardium during exercise is largely served by an increase in coronary blood flow. Accordingly, peak values of coronary blood flow in dynamic exercise are three to five times the resting level (10), an increase that is influenced by the interaction between the relaxing myocardium and decompression of small intramycocardial blood vessels, which can be quantified using the backward decompression wave. This has been described in animal models (40) and in humans (6, 23). We therefore sought to demonstrate an appropriate response in noninvasive wave intensity with exercise.

We found that coronary wave intensity can be assessed in most patients at moderate levels of exertion; in a proportion of patients, it can even be gauged at more intense levels. With exercise, there is an appropriate progressive increase in the magnitude of the backward decompression wave. This reflects
the increased “suction” effect of the myocardium on the coronary circulation with increasing oxygen demand. In turn, this results in a measurable increase in coronary flow rate and blood supply. Peak and cumulative backward decompression wave intensity were increased three to fourfold during exercise, which is similar in magnitude to that reported in other studies (5, 23).

Applications. The use of this technique has a wide variety of applications in disease states. With moderate expertise, it can be measured in the majority of patients, carries no risk, and requires no pharmacological agents. Therefore, its key feature is in its ability to perform serial measurements in the interrogation of patients who have insufficient clinical indication to undergo angiography or for follow-up in those who have had invasive assessment.

Previous work has demonstrated that patients with aortic stenosis have a strikingly abnormal wave-intensity profile that normalizes immediately following valve implantation (5). Using noninvasively derived measures of wave intensity may permit a further measure of myocardial burden to be estimated in patients with mild or moderate aortic stenosis and thus aid the timing of intervention. Similarly, in patients with other cardiomyopathies where noninvasively derived CFR can predict outcome (3, 33) this marker may allow further risk stratification and monitoring of the effect of therapy.

Given that noninvasively measured wave intensity is able to recognize subtle resting abnormalities in myocardial function, it is also possible that it may have potential as a preclinical screening tool in patients with risk factors for cardiovascular disease. In those at risk with an abnormal resting wave-intensity profile, treatment could be instigated early and followed to ensure normalization.

The ability to apply this technique to patients undergoing exercise opens further avenues to assess disease states during exertion. In particular, valve disorders or progressive cardiomyopathic conditions could be serially assessed during exercise to allow timing of intervention. In patients unable to exercise, a pharmacological stressor could be applied to provide similar results. The majority of the technical difficulties in measuring noninvasive exercise coronary wave intensity were actually due to the movement of the body while pedaling particularly at higher levels of exertion. Therefore, with use of handgrip isometric exercise, it may possible to make this assessment easier, and given the sensitivity of WIA, only a moderate heart rate increase may be required.

Disadvantages and limitations. In this study, the measurement of noninvasive WIA was not performed exactly at the same time as the invasive assessment but rather was undertaken serially within 30 min of the procedure. However, patients remained supine between these two recordings and there was no marked change in heart rate, coronary flow rate, or pharmacological state of the patient and they remained supine on the bed.

We assumed aortic pressure would be an acceptable surrogate of the LAD pressure waveform. This assumption is the basis of pressure-based assessment of moderate coronary lesions (31, 38), and we demonstrated similar waveform shapes of noninvasive central and invasive aortic and coronary pressure using cross-correlation coefficients. However, recent data (4, 30) have suggested a systematic error in central pressure estimation due to the Pulsocor’s calibration using brachial pressures, and similar biases have been reported for other noninvasive devices (9). It has been suggested that calibration to mean and diastolic pressure may minimize this bias (4) and this issue should be addressed in future studies. While wave intensity employs the derivatives of the pressure and flow waveforms so the impact of a blood pressure calibration error on estimated wave intensity is likely to be modest, consistent with this we found that minimum dP/dt and peak and cumulative wave intensity estimated noninvasively were lower than invasive measures. For the backward-traveling decompression wave, the resultant difference in wave intensity was small (~10%), but for other more minor waves the differences were larger. The errors introduced by calibration to brachial pressures may also account for the lower wave speeds measured noninvasively. These issues should therefore be considered in studies aiming to measure coronary wave intensity using noninvasive methods.

There are several other alternative approaches to assess central pressure noninvasively including tonometric techniques. These techniques are also hampered by some of the issues faced by oscillometric devices (37) and appear to provide data of a similar accuracy. Despite this, future work should also focus on establishing the potential role of these devices in the estimation of wave intensity.

No intracoronary nitrates were used during invasive assessments in this study. While the physical presence of an intracoronary wire may cause a degree of coronary spasm, we felt the impact of intracoronary nitrates on wave speed and wave intensity (7, 8, 36) would be more confounding as this could not be replicated during the noninvasive assessment. Additionally, the presence of the coronary wire itself will also affect flow, albeit modestly (ultimately favoring noninvasive coronary wave intensity as the most accurate form of assessment). However, none of the patients included in this study had any angiographic evidence of coronary spasm during intracoronary wire assessment.

The major technical limitation with the application of this technique is the fact that coronary imaging by echocardiography requires training and is challenging to achieve in some
CONSTRUCTION OF NONINVASIVE CORONARY WIA

patients as demonstrated by the failure to accurately assess coronary flow in five of the recruited patients. However, this is probably similar to the level of expertise required to use the invasive pressure-flow wire and with practice, in the hands of a skilled echocardiographer, measurements can be reliably made in the majority of patients (35) particularly with the widespread availability if used with contrast.

Finally, we recognize that while we were able to accurately measure the backward decompression wave, the other waves in the cardiac cycle were underestimated. However, given the good correlation between invasive and noninvasive backward decompression wave energy fraction, relative changes in this value would remain clinically relevant. Additionally, the backward decompression wave has consistently shown itself to be the most clinically relevant wave (6, 7, 18, 23, 39).

Conclusion. It is possible to measure coronary wave intensity in the LAD using widely available noninvasive technology. This method provides an acceptably accurate assessment of the backward decompression wave under resting conditions. The technique has sufficient sensitivity to detect changes associated with left ventricular hypertrophy and exercise. It enhances the applicability of coronary wave intensity to larger cohort-based studies where invasive pressure and flow would be unethical or unpractical to obtain to provide greater understanding of myocardial–coronary interaction. It also provides an opportunity to conveniently and safely make repeated measurements following a range of pharmacological (and other) interventions.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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