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Estimation of coronary wave intensity analysis using non-invasive techniques and its application to exercise physiology

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Abstract

Introduction: Wave intensity analysis (WIA) has found particular applicability in the coronary circulation where it can quantify travelling waves that accelerate and decelerate blood flow. The most important wave for the regulation of flow is the backward-travelling 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 non-invasively. In this study we set out to assess the agreement between invasive and non-invasive coronary WIA at rest and measure the effect of exercise.

Method and Results: 22 patients (mean age 60) with unobstructed coronaries underwent invasive WIA in the Left Anterior Descending artery (LAD). Immediately afterwards, non-invasive 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 non-invasive coronary WIA assessment during exercise.

A pattern of 6 waves were observed in both modalities. The BDW was similar between invasive and non-invasive measures (peak: 14.9±7.8 vs -13.8±7.1x10^4 $Wm^{-2}s^{-2}$, concordance correlation coefficient (CCC) 0.73, $p<0.01$; cumulative -64.4±32.8 vs -59.4±34.2x10^2 $Wm^{-2}s^{-1}$, CCC 0.66, $p<0.01$), but smaller waves were underestimated non-invasively. Increased left ventricular mass correlated with a decreased non-invasive BDW fraction ($r=-0.48$, $p=0.02$). Exercise increased the BDW: at maximum exercise peak BDW was -47.0±29.5x$10^4$$Wm^{-2}s^{-2}$ ($p<0.01$ vs rest) and cumulative BDW -19.2±12.6x10^3 $Wm^{-2}s^{-1}$ ($p<0.01$ vs rest).

Conclusion: The BDW can be measured non-invasively with acceptable reliably potentially simplifying assessments and increasing the applicability of coronary WIA.

Key words: artery, blood flow, physiology, hypertrophy, microcirculation

Note and noteworthy

Coronary wave-intensity analysis can be measured non-invasively 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 sub-groups.

Introduction

Wave intensity analysis (WIA) provides a time-domain separation of up- and down-stream 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 (BDW), 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), increased in severe aortic stenosis(5), increases in response to pacing(40) or exercise(23) and can be used to predict myocardial recovery after infarction(39).

Whilst many peripheral arteries are amenable to interrogation using non-invasive 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 non-invasively 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 non-invasive 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.

Glossary

c – wavespeed

CCC – Lin's correlation coefficient of concordance

CFR – Coronary Flow Reserve

ECG – ElectroCardioGram

iFR – instantaneous wave-free ratio

LAD – Left Anterior Descending artery

Pa – Proximal pressure

Pd – Distal pressure

PdPa – Pd to Pa ratio

PRF – Pulse Repetition Frequency

SD – Standard Deviation

WIA – Wave Intensity Analysis

$WI_{+/-/NET}$ – Wave Intensity proximal / distal / net

ρ – density of blood (1050 kg m^{-3})

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 ischaemic 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 Research Ethics Committee and all subjects gave written informed consent (11/LO/1454).

Invasive pressure and flow measurements

Cardiac catheterisation was performed via either the femoral or radial approach. After diagnostic angiography, studies were closely inspected by 2 operators and only patients with angiographically normal arteries proceeded to have haemodynamic 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-inch diameter combined pressure- and flow-tipped wire (Combowire, Volcano Therapeutics, Inc) passed into the mid-LAD and manipulated until an optimal flow and pressure signal were obtained. Pressure and flow data was recorded using a Combomap console (Volcano Therapeutics, Inc) over a period of one minute.

Non-invasive pressure and flow measurements

Immediately following completion of angiography and exit from the coronary catheter laboratory non-invasive coronary flow and pressure waveforms were obtained. Echocardiography was performed using either a Phillips ie33 (Amsterdam, 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 PRF typically in the range of 15-25cm/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 less than 20^{o} to the probe. Pulse wave Doppler was applied with a sampling width of 7.5-10mm and multiple coronary flow signals 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 was 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 recognised by the Pulsecor system's quality-control) was repeated. Each waveform was then aligned according to the peak negative dP/dt before ensemble-averaging in order to prevent over-smoothing of the early diastolic section of the pressure waveform which is essential for the construction of the backward decompression wave.

Non-invasive 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 ECG-gating accounting for the inherent Combomap flow-pressure offset (mean number of cardiac cycles 63±58).

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

Wave-intensity analysis

Wavespeed (c) was calculated using the single-point method(8). Wave-intensity analysis was calculated as previously described(7). Briefly, we used the product of the first time derivatives of pressure (dP/dt) and velocity (dU/dt) 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:

$$WI_+ = \frac{1}{4\rho c}\left[\frac{dP}{dt} + \rho c\left(\frac{dU}{dt}\right)\right]^2$$

$$WI_- = -\frac{1}{4\rho c}\left[\frac{dP}{dt} - \rho c\left(\frac{dU}{dt}\right)\right]^2$$

$$WI_{NET} = WI_+ WI_- = \left(\frac{dP}{dt}\right)\left(\frac{dU}{dt}\right)$$

where ρ is the density of blood (taken as 1050 kg m^{-3})

To separate coincident waves from proximal and distal origins the change in pressure was separated into its wave components: dP_+/dt(proximal) and dP_-/dt(distal).

$$\frac{dP_+}{dt} = {}^1\!/_2\left(\frac{dP}{dt} + \rho c\left(\frac{dU}{dt}\right)\right)$$

$$\frac{dP_-}{dt} = {}^1\!/_2\left(\frac{dP}{dt} - \rho c\left(\frac{dU}{dt}\right)\right)$$

Cumulative wave intensity (i.e. wave energy) was calculated for each wave by measuring the area under the peak of the wave intensity versus 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').

Non-invasive coronary wave intensity analysis in exercise

A subgroup of 10 patients went on to have non-invasive 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 hours prior to attendance and avoid alcohol, nicotine or nitrates in the preceding 24 hours.

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

Reproducibility

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

Statistics

The data was analysed using STATA 11 and Matlab R2015a. Continuous variables are reported as mean ± standard deviation (SD). The Bland-Altman method was used to quantify agreement between non-invasive and invasive wave-intensity and to analyse 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 standard deviation of difference between measures to the mean value of the measure. 2-dimensionsal cross-correlation coefficients were used as a measure of similarity between non-invasive and invasive waveforms. Invasive and non-invasive values were compared using a Wilcoxon matched-pairs signed-ranks test. Exercise haemodynamic data was analysed 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. A p value of less than 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 (14 male). Systolic function was preserved (mean ejection fraction 59%) with no significant valvular disorders. Risk factors for coronary disease included hypercholesterolaemia (58%), hypertension (35%), diabetes (6%) and smoking (6%) (Table 1). Echocardiographic data are displayed in Table 2.

Haemodynamic data

Maximum coronary flow velocities were similar in the invasive and non-invasive groups but minimum velocity was higher by non-invasive methods (Table 3). Invasive systolic and mean pressure was higher by invasive methods, although diastolic pressure did not differ (Table 3). Mean cross-correlation coefficients between invasively measured Pa (aorta - catheter tip) and Pd (coronary wire pressure) were 0.99±0.00. Mean resting Pd/Pa was 1.0 ± 0.03 and iFR 0.99 ± 0.03. The minimum dP/dt was higher invasively than non-invasively (-0.57±0.21 vs. -0.36±0.16 mmHg.s-1; $p<0.01$) but with a favourable concordance (CCC=0.44, $p<0.01$); additionally the mean cross-correlation coefficient between invasive and non-invasive pressure waveforms was very high ($r = 0.99\pm0.01$). The time of minimum dP/dt from the foot of the systolic aortic upstroke was 305ms invasively and 281ms non-invasively ($p = 0.02$).

As previously described, 6 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 (Figure 1).

Peak backward decompression wave was -14.9±7.8x10^4 $Wm^{-2}s^{-2}$ invasively and -13.8±7.1x10^4 $Wm^{-2}s^{-2}$ non-invasively and measures showed good concordance (CCC 0.73, p<0.01). Cumulative wave intensity was -64.4±32.8x10^2 $Wm^{-2}s^{-1}$ invasively compared to -59.4±34.2x10^2 $Wm^{-2}s^{-1}$ non-invasively (CCC 0.66, p<0.01) (Figure 2, Table 3).

The non-invasive measures of other waves underestimated their magnitude compared with invasive measures (Table 3). This meant the fraction backward decompression wave intensity was higher in the non-invasive group (29.7±9.5% non-invasively 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 non-invasive methods (Table 3). As previously reported(4), a correlation was also seen between the non-invasive 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±2.0mmHg (CV= 2.4%). The mean±SD of the difference between the separate 30-s recordings of flow velocity was 0.7±0.7 cms^{-1} (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 x 10^2 $Wm^{-2}s^{-1}$ (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 x10^{-4} $Wm^{-2}s^{-2}$ (CV = 4.4%).

Left Ventricular mass

Mean left ventricular mass was 163±37g with 5 patients meeting the definition of left ventricular hypertrophy(19). There was a significant negative correlation between left ventricular mass and both non-invasive (r=-0.48, p=0.02, Figure 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 and the non-invasive 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 sub analysis because of technically-inadequate coronary flow sampling during exertion. Peak coronary flow rose during exercise from 23.2±8.2 cm/s to 42.2±17.8 cm/s (p<0.01 for trend) as did systolic pressure (120±13.0 to 140±23.4 mmHg, p=0.07 for trend). Diastolic pressure rose only modestly from 82.3±10.5 to 85.9±11.0mmHg (p=0.68 for trend).

Both peak and cumulative backward decompression wave demonstrated a progressive increase with exercise. Peak was -9.7±6.3 x 10^4 $Wm^{-2}s^{-2}$ at baseline and increased to -12.5±6.3 x10^4 $Wm^{-2}s^{-2}$ at moderate exercise and -47.0±29.5 x 10^4 $Wm^{-2}s^{-2}$ at peak (z=-3.33, p<0.01 for trend). Cumulative was -4.3±3.2 x10^3 $Wm^{-2}s^{-1}$ at rest and rose to -6.6±3.3 x 10^3 $Wm^{-2}s^{-1}$ at moderate exercise and -19.2±12.6 x 10^3 $Wm^{-2}s^{-1}$ at peak (z=-3.80, p<0.01 for trend) (Figure 4 & 5, Table 4).

Discussion

We have demonstrated that the coronary wave intensity profile can be measured with reasonable fidelity non-invasively 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 non-invasively was good, the correlation between the backward decompression wave and LV mass was similar between invasive and non-invasive methods, and exercise induced a graded increase in the backward decompression wave intensity demonstrating the sensitivity of this non-invasive method to a physiological intervention.

Non-invasive measures of flow, pressure and wave-intensity

With the introduction of newer echocardiography machines with 2nd 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 in order to assess microvascular dysfunction with varying degrees of success. To that end, correlates have been recognised between invasively measured systolic flow reversal(41), diastolic deceleration time(15, 20) and recovery after myocardial infarction and these markers have been adopted non-invasively as well(29). Combining non-invasive pressure and flow data to calculate coronary wave intensity offers a potentially valuable index of coronary haemodynamics.

The derivation of wave-intensity from pressure and flow tracings has previously been successfully performed non-invasively 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 left anterior descending artery using non-invasive 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 prior to ensembling and optimised 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 co-registration 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 recognised 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 LV mass is associated with adverse cardiovascular outcomes(12, 21). CFR is reduced with left ventricular hypertrophy(13), a feature which is reversible with therapy(27) so that despite an increased muscle mass, the ability of the heart to regulate its own blood 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 non-invasive method for measuring coronary wave intensity with acceptable accuracy.

Whilst only 5 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 wave-intensity analysis. We would therefore anticipate a correlation between left ventricular mass and wave-intensity even when LV mass is within the 'normal' range and this is indeed what we found.

Exercise Physiology

At rest, haemoglobin concentration and oxygen extraction of coronary flow are already at 70-80% maximum capacity and therefore the resultant 5-fold 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 3-5 times the resting level(10), an increase that is influenced by the interaction between the relaxing myocardium and decompression of small intra-myocardial 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 non-invasive 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 3-4 fold 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 whom have had invasive assessment.

Previous work has demonstrated that patients with aortic stenosis have a strikingly abnormal wave-intensity profile that normalises immediately following valve implantation(5). Using non-invasively 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 non-invasively derived CFR can predict outcome(3, 33) this marker may allow further risk stratification and monitoring of the effect of therapy.

Given that non-invasively measured wave intensity is able to recognise subtle resting abnormalities in myocardial function it is also possible that it may have potential as a pre-clinical 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 normalisation.

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 non-invasive exercise coronary wave-intensity were actually due to the movement of the body whilst pedalling 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 wave-intensity analysis, only a moderate heart rate increase may be required.

Disadvantages and Limitations

In this study, the measurement of non-invasive WIA was not performed exactly at the same time as the invasive assessment but rather was undertaken serially within 30 minutes 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 non-invasive 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 Pulsecor's calibration using brachial pressures, and similar biases have been reported for other non-invasive 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. Whilst wave intensity employs the derivatives of the pressure and flow waveforms so the impact of a BP calibration error on estimated wave intensity is likely to be modest, consistent with this we found that minimum dP/dt, peak and cumulative wave intensity estimated non-invasively was lower than invasive measures. For the BDW the resultant difference in wave intensity were 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

372 measured non-invasively. These issues should therefore be considered in studies aiming to measure
373 coronary wave intensity using non-invasive methods.

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

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

386 The major technical limitation with the application of this technique is the fact that coronary imaging
387 by echocardiography requires training and is challenging to achieve in some patients as
388 demonstrated by the failure to accurately assess coronary flow in five of the recruited patients.
389 However, this is probably similar to the level of expertise required to use the invasive pressure-flow
390 wire and with practice, in the hands of a skilled echocardiographer, measurements can be reliably
391 made in the majority of patients(35) particularly with the widespread availability if used with
392 contrast.

393 Finally we recognise that whilst we were able to accurately measure the backward decompression
394 wave, the other waves in the cardiac cycle were underestimated. However, given the good
395 correlation between invasive and non-invasive 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 left anterior descending artery using widely available non-invasive 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

The authors report no disclosures.

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Tables

DEMOGRAPHIC		VALUE
Age (yr)		60 ± 12
Male (%)		14 (64)
Height (cm)		171 ± 12
Weight (kg)		85.5 ± 17
BMI (kg/m^2)		29.1 ± 3.9
Hypertensive (%)		8 (36)
Cholesterol therapy (%)		12 (55)
DM (%)		1 (5)
Current smoker (%)		1 (5)
Pharmacological therapy	Beta blocker (%)	3 (14)
	Ace Inhibitor / Angiotensin Receptor Blocker (%)	6 (27)
	Calcium channel antagonist (%)	4 (18)
	Thiazide diuretic (%)	2 (9)
	Alpha blocker (%)	1 (5)
	Aspirin (%)	12 (55)
	Statin (%)	12 (55)

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

MEASUREMENT		
2D measurements (cm)	LVEDd	4.5 ± 0.5
	LVEDs	3.0 ± 0.7
	IVSd	1.04 ± 0.21
	PWd	1.02 ± 0.21
	IVSs	1.6 ± 0.43
	PWs	1.7 ± 0.43
Mitral inflow (cm/s)	E	65.5 ± 16
	A	68.5 ± 17
Mean tissue doppler (cm/s)	e'	9.4 ± 3.3
	s'	8.7 ± 3.1
	E/A	0.96 ± 0.22
	E/e’	7.0 ± 2.9
LV mass (g)		163 ± 37

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

Values are mean ± SD.

		Non-invasive	Invasive	Difference	CCC*	p†	p‡
Heart rate(bpm)		60.4±9.0	63.9±9.5	3.5±4.5	0.74	<0.01	0.3
Wave speed		14.7±4.5	17.9±8.0	3.2±2.2	0.41	<0.01	0.01
Cumulative wave intensity $x10^2$ $Wm^{-2}s^{-1}$	Forward compression wave	44.9±16.9	62.6±24.1	17.7±38.3	-0.01	0.9	0.04
	Forward decompression wave	3.6±5.2	25.6±19.0	22.0±16.0	-0.03	1.0	<0.01
	Backward decompression wave	-59.4±34.2	-64.4±32.8	5.0±3.4	0.66	<0.01	0.2
	Backward decompression wave energy fraction (%)	29.7±9.5	22.1±5.4	7.6±9.9	0.27	0.04	<0.01
Peak wave intensity $X10^4$ $Wm^{-2}s^{-2}$	Forward compression wave	7.7±3.8	24.5±11.7	16.8±14.7	0.01	0.8	<0.01
	Forward decompression wave	4.6±5.2	9.8±7.4	5.2±5.7	0.05	0.9	<0.01
	Backward decompression wave	-13.8±7.1	-14.9±7.8	1.1±5.5	0.73	<0.01	0.9
Coronary flow velocity, cm/s	Peak velocity	29.2 ± 6.5	29.1 ± 10.1	0.1±0.1	0.49	<0.01	0.6
	Mean velocity	17.5 ± 4.3	17.2 ± 6.7	0.3±0.6	0.42	<0.01	0.1
	Minimum velocity	11.3 ± 3.1	7.45 ± 4.1	3.9±0.5	0.15	0.30	0.02
Central pressure, mmHg	Systolic mmHg	122 ± 16.2	127 ± 21.2	5.0±7.7	0.45	<0.01	<0.01
	Diastolic mmHg	77.4 ± 9.4	75.2 ± 9.4	2.2±2.3	0.65	<0.01	0.5
	Mean mmHg	91.1 ± 10.6	92.2 ± 12.1	1.1±1.0	0.37	<0.01	<0.01

Table 3. Invasive versus non-invasive coronary haemodynamics.

*Lin's concordance correlation coefficient (CCC) and †p value for the significance of this value. p values for direct comparison are also displayed (p‡).

Values are mean ± SD.

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	Baseline	Mid-exercise	Peak-exercise	P value for trend
Heart Rate (bpm)	72.3 ± 9.8	84.8 ± 11.3	102.4 ± 9.7	<0.01
Systolic pressure (mmHg)	120 ± 13.0	128 ± 19.6	140 ± 23.4	0.07
Diastolic pressure(mmHg)	82.3 ± 10.5	86.7 ± 10.5	85.9 ± 11.0	0.68
Peak velocity (cm/s)	23.2 ± 8.2	31.2 ± 12.0	42.2 ± 17.8	<0.01
Minimum velocity (cm/s)	8.5 ± 2.4	10.3 ± 4.3	12.4 ± 4.5	0.07
Peak backward decompression wave ($Wm^{-2}s^{-2}$ $x10^4$)	-9.7 ± 6.3	-12.5 ± 6.3	-47.0 ± 29.5	<0.01
Cumulative backward decompression wave ($Wm^{-2}s^{-1}$ x 10^3)	-4.3 ± 3.2	-6.6 ± 3.3	-19.2 ± 12.6	<0.01

613

614 **Table 4. Coronary haemodynamic data during graded exercise in 9 patients**

615

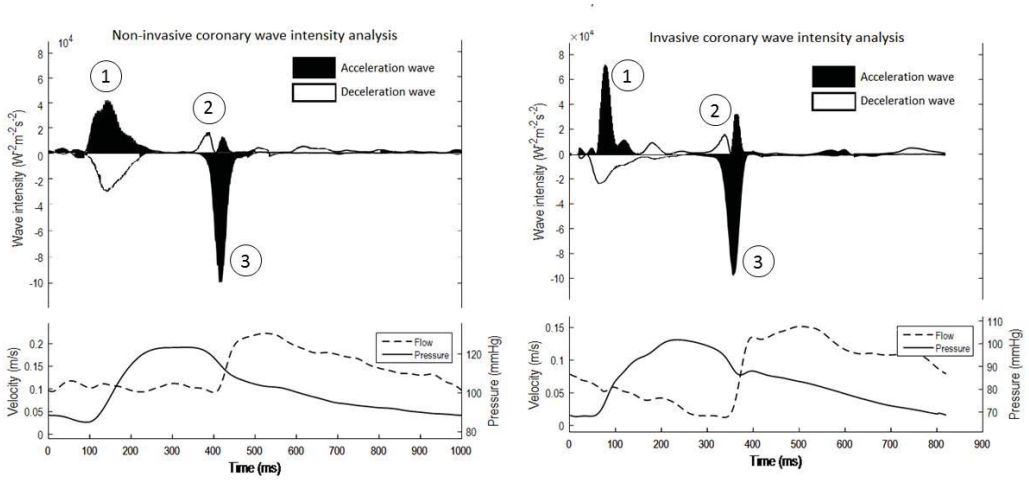

Figure 1. Invasive versus non-invasive wave intensity analysis. 6 waves were identified through both modalities.

The three 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 re-expansion of the intra-myocardial vessels that were compressed during systole Whilst the other waves of the cardiac cycle are underestimated non-invasively a good concordance is seen with backward decompression wave

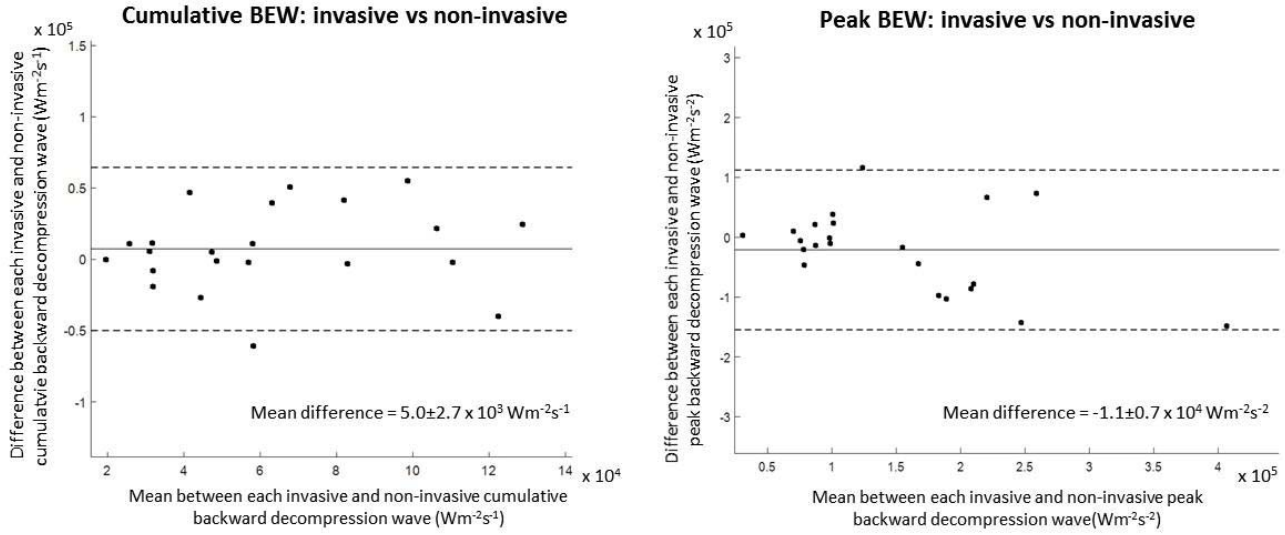

Figure 2. Bland Altman plot of invasive versus non-invasive backward decompression wave: peak (left) and cumulative (right),

Solid horizontal line represents mean difference and dashed lines the limit of agreement (±1.96x SD).

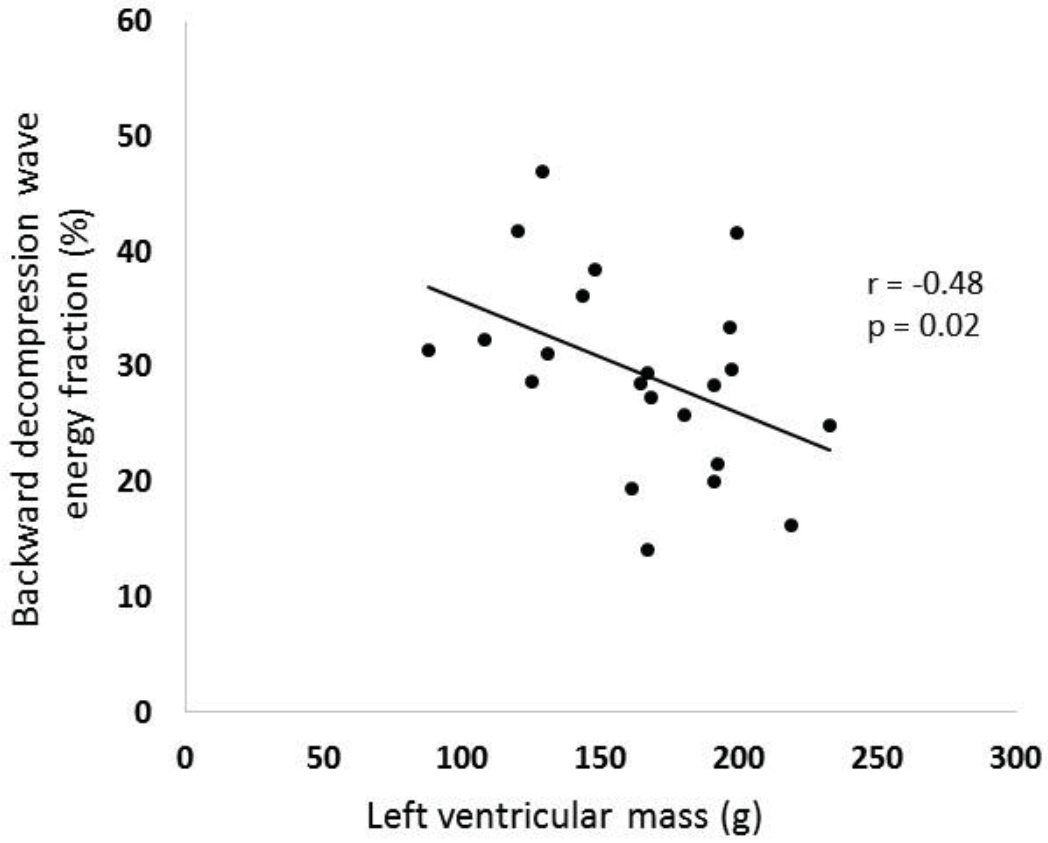

Figure 3. Scatterplot showing the relationship between the non-invasive backward decompression wave energy fraction and left ventricular mass.

The solid line represents the regression line and Pearson's correlation coefficient is shown.

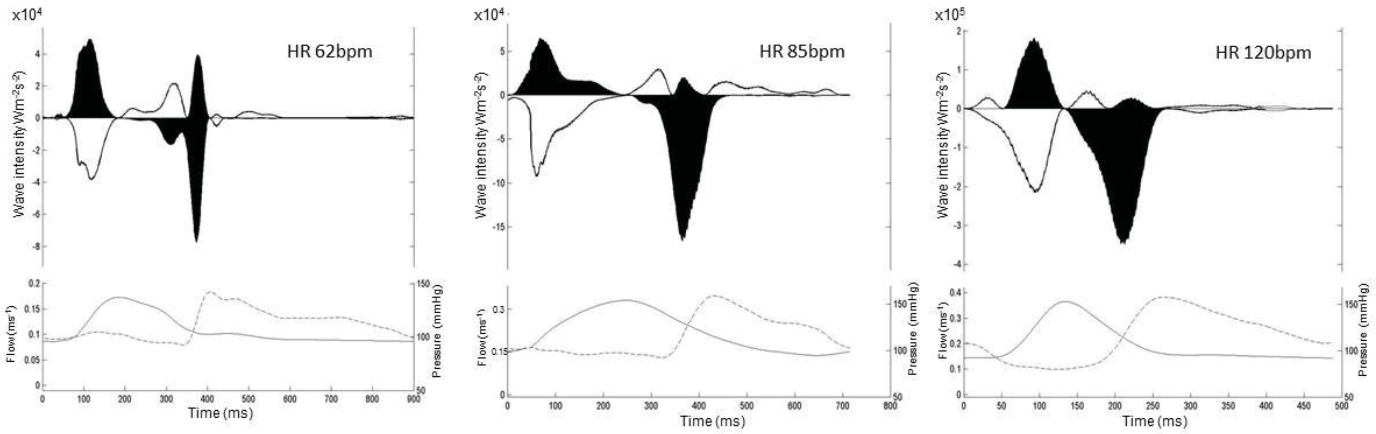

Figure 4. Coronary flow assessment and non-invasive wave-intensity analysis at increasing heart rates.

Rest is displayed on the left, mid-exertion centrally and maximum exertion on the right. With exercise and a resultant increasing heart rate a progressive increase is seen in the in size of the cumulative and peak backward decompression wave. This reflects a greater 'suction' effect from the myocardium resulting in higher coronary flow rates per cardiac cycle. HR = Heart Rate. Note, both flow, blood pressure

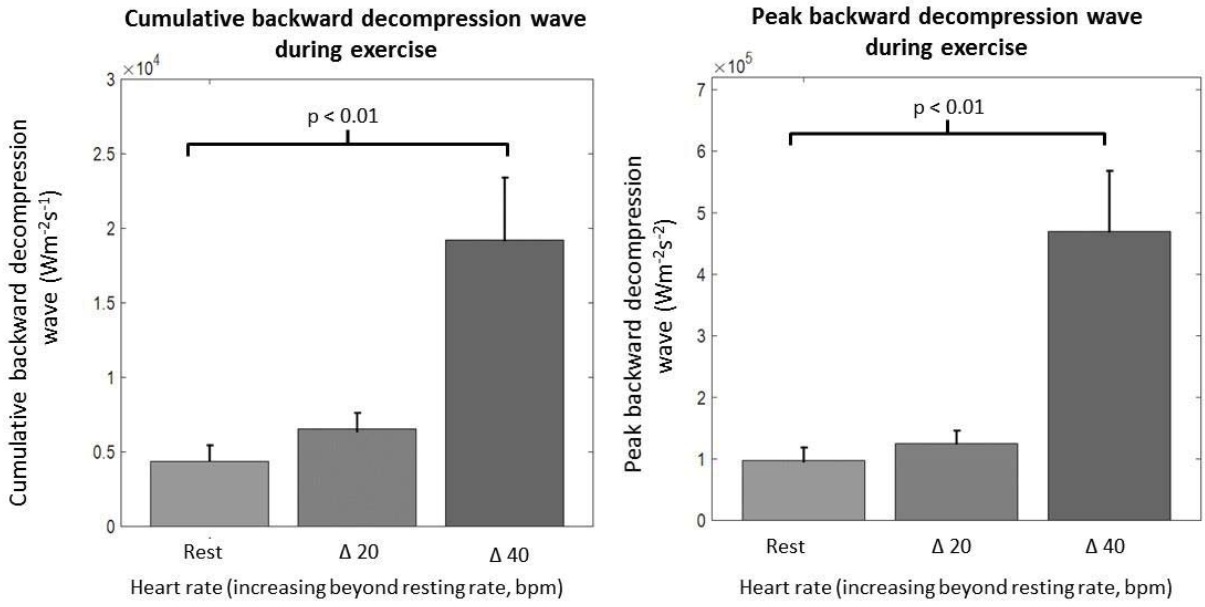

Figure 5. Peak and cumulative backward decompression wave with exercise.

With exercise there is a progressive increase in the peak and cumulative backward decompression wave (data displayed as mean and standard error of the mean with p value for trend).

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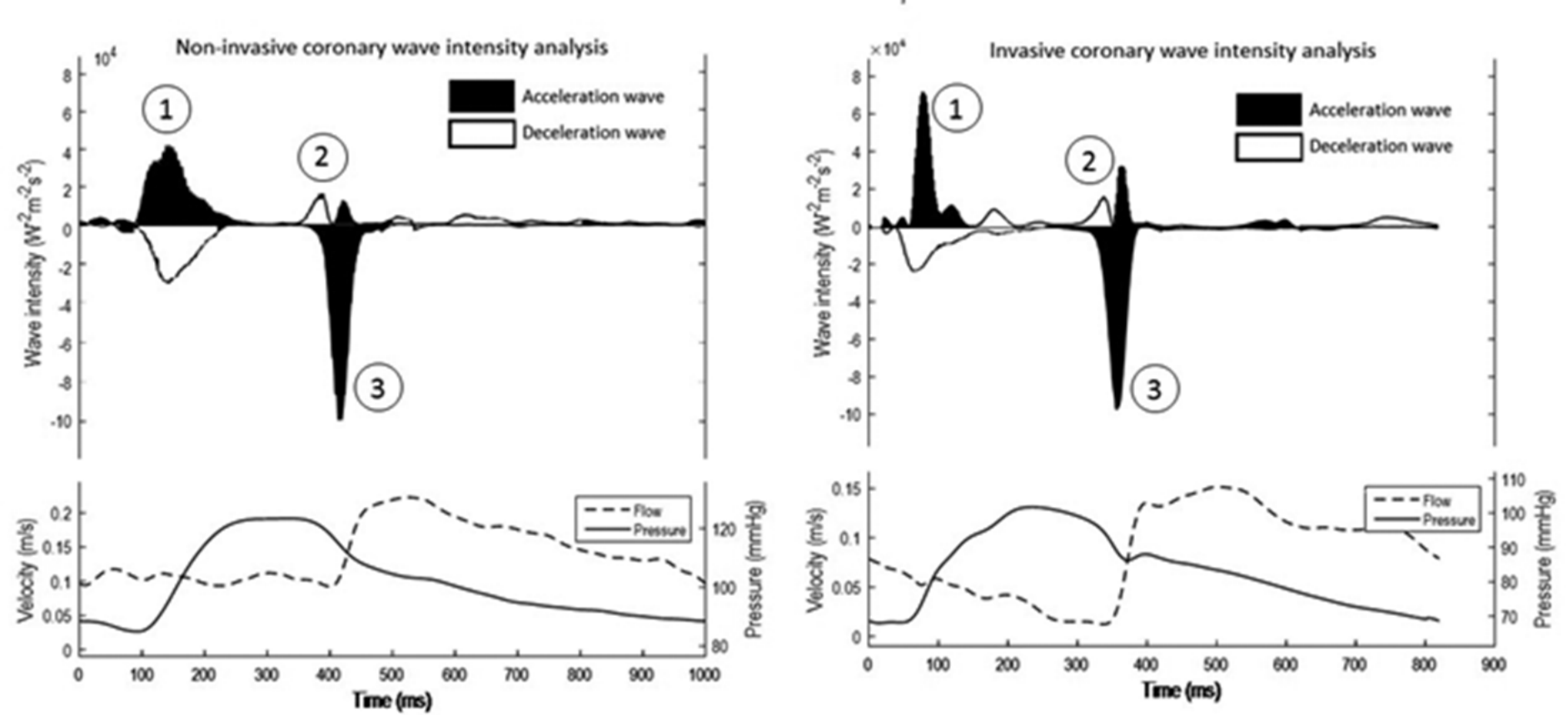
Non-invasive coronary wave intensity analysis
Acceleration wave
Deceleration wave
Wave intensity (W²m⁻²s⁻²)
Velocity (m/s)
Pressure (mmHg)
Flow
Pressure
Time (ms)
Invasive coronary wave intensity analysis
Acceleration wave
Deceleration wave
Wave intensity (W²m⁻²s⁻²)
Velocity (m/s)
Pressure (mmHg)
Flow
Pressure
Time (ms)

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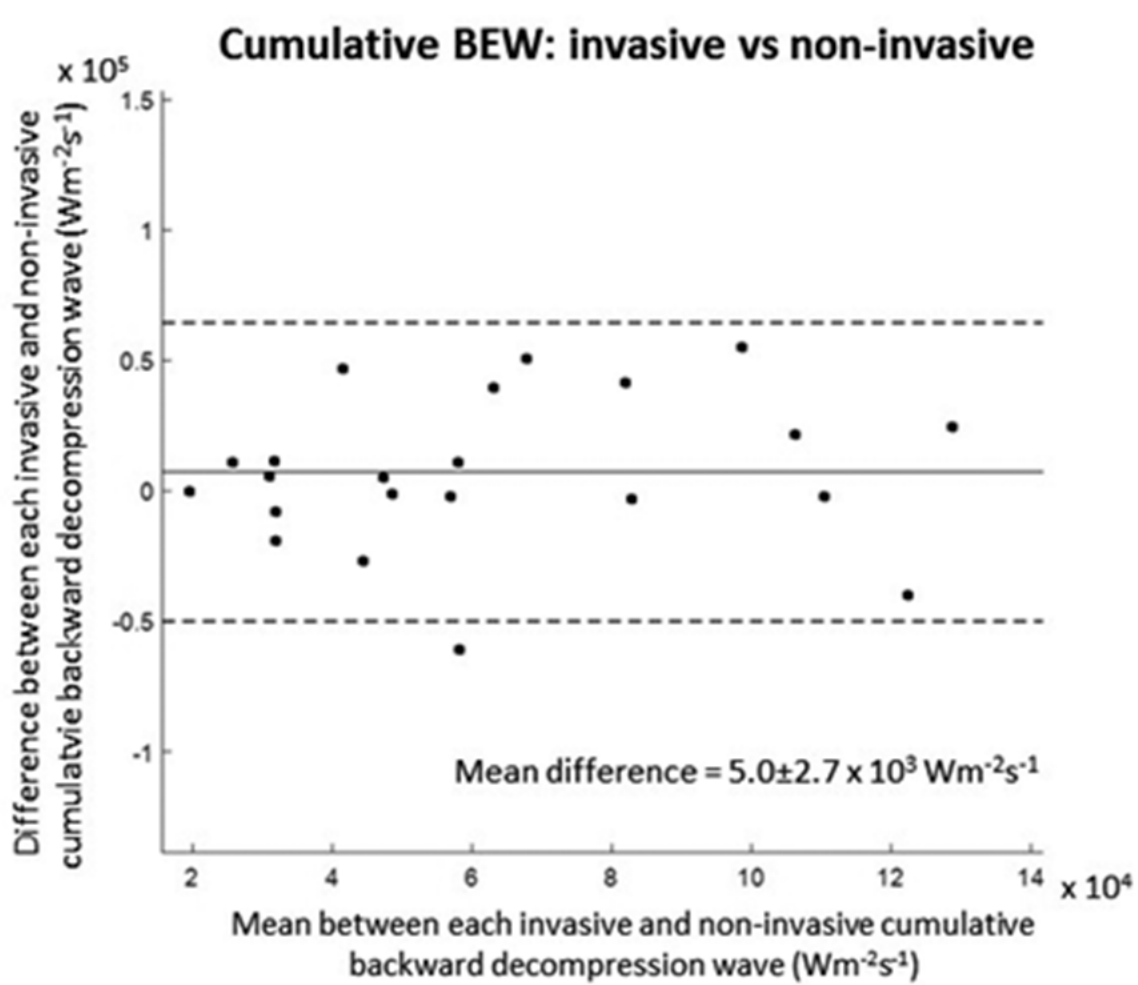
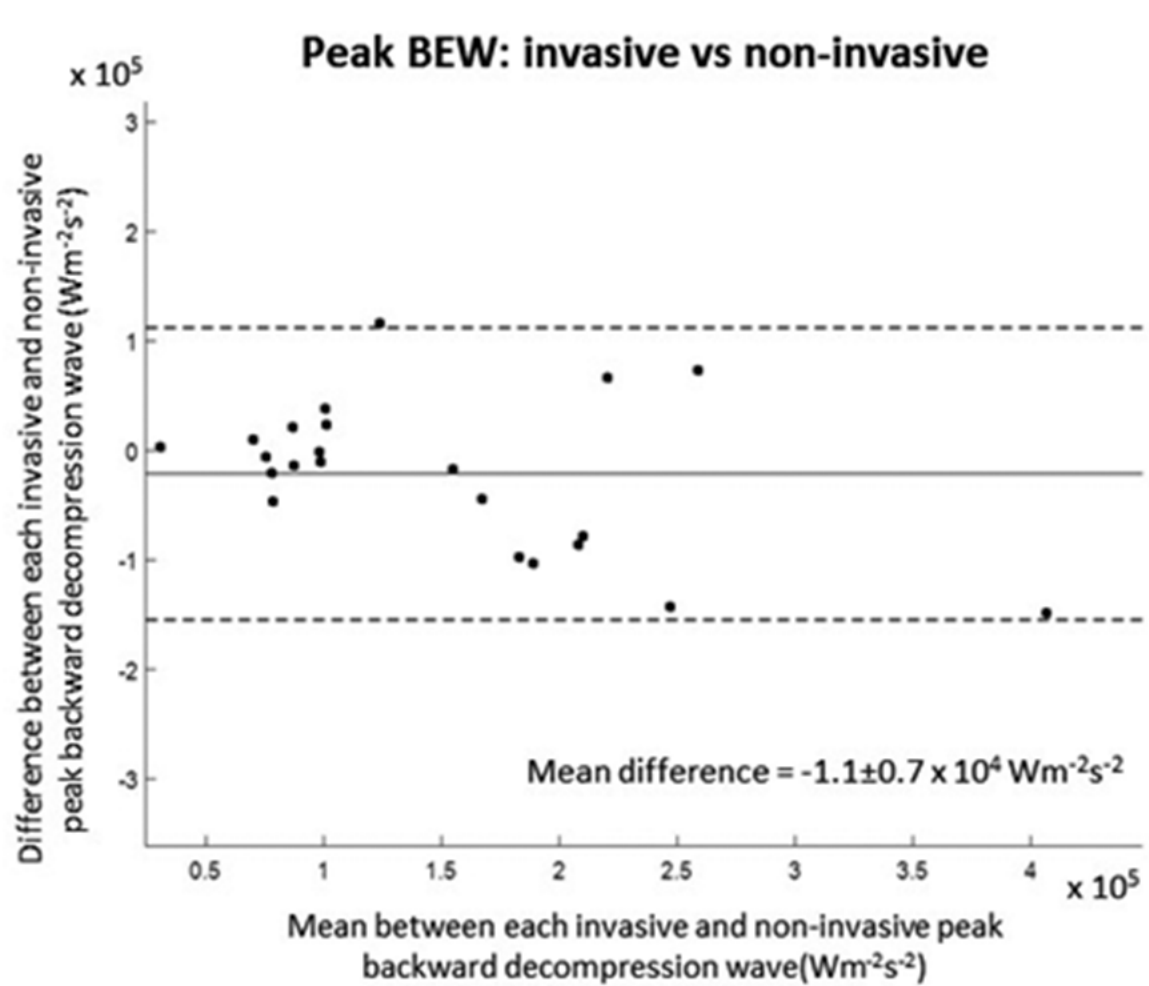

Cumulative BEW: invasive vs non-invasive
x 10^5
1.5
1
0.5
0
-0.5
-1
Difference between each invasive and non-invasive cumulatvie backward decompression wave (Wm^-2s^-1)
Mean difference = 5.0±2.7 x 10^3 Wm^-2s^-1
2
4
6
8
10
12
14
x 10^4
Mean between each invasive and non-invasive cumulative backward decompression wave (Wm^-2s^-1)


Peak BEW: invasive vs non-invasive
x 10^5
3
2
1
0
-1
-2
-3
Difference between each invasive and non-invasive peak backward decompression wave (Wm^-2s^-2)
Mean difference = -1.1±0.7 x 10^4 Wm^-2s^-2
0.5
1
1.5
2
2.5
3
3.5
4
x 10^5
Mean between each invasive and non-invasive peak backward decompression wave(Wm^-2s^-2)

Type of file: figure
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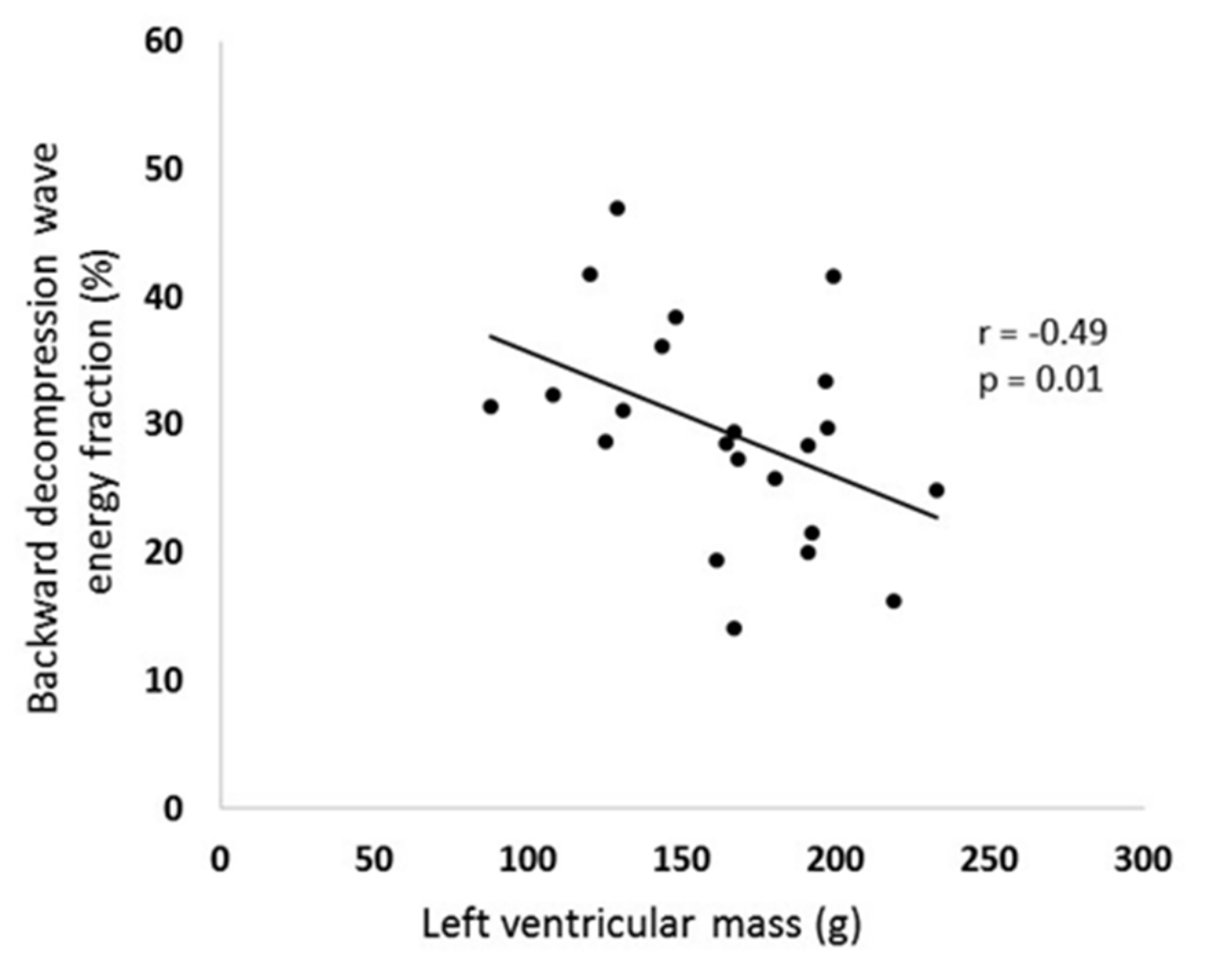
60
50
40
30
20
10
0
Backward decompression wave energy fraction (%)
r = -0.49
p = 0.01
0
50
100
150
200
250
300
Left ventricular mass (g)

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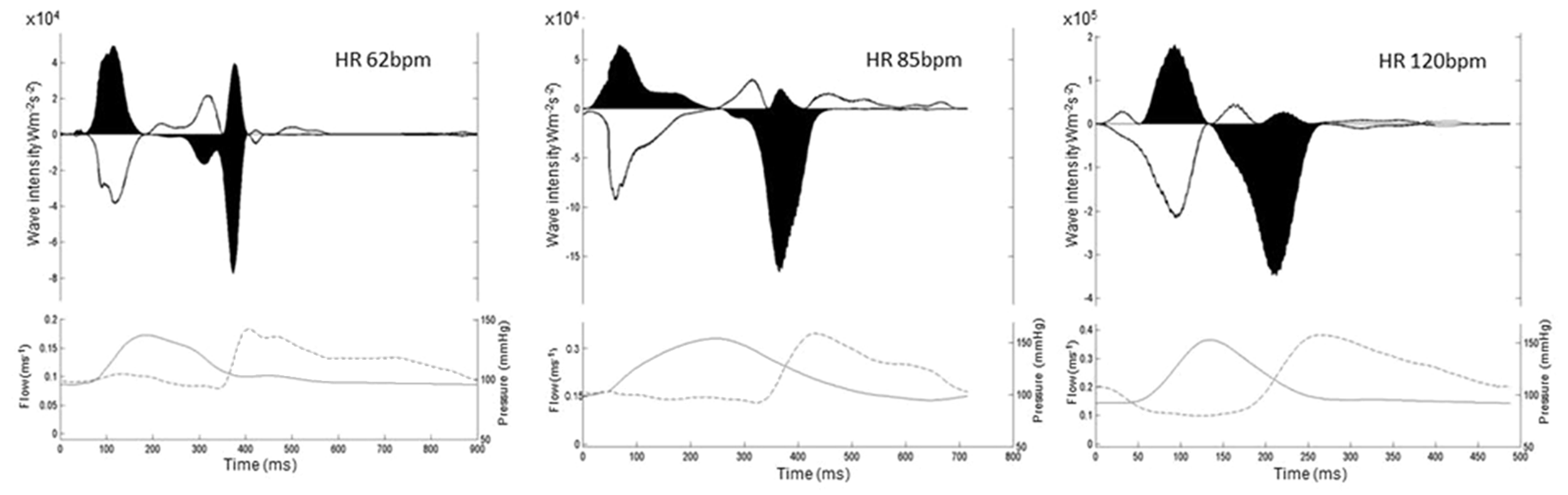
HR 62bpm
HR 85bpm
HR 120bpm
Wave intensity Wm-2s-2
Flow (ms-1)
Pressure (mmHg)
Time (ms)

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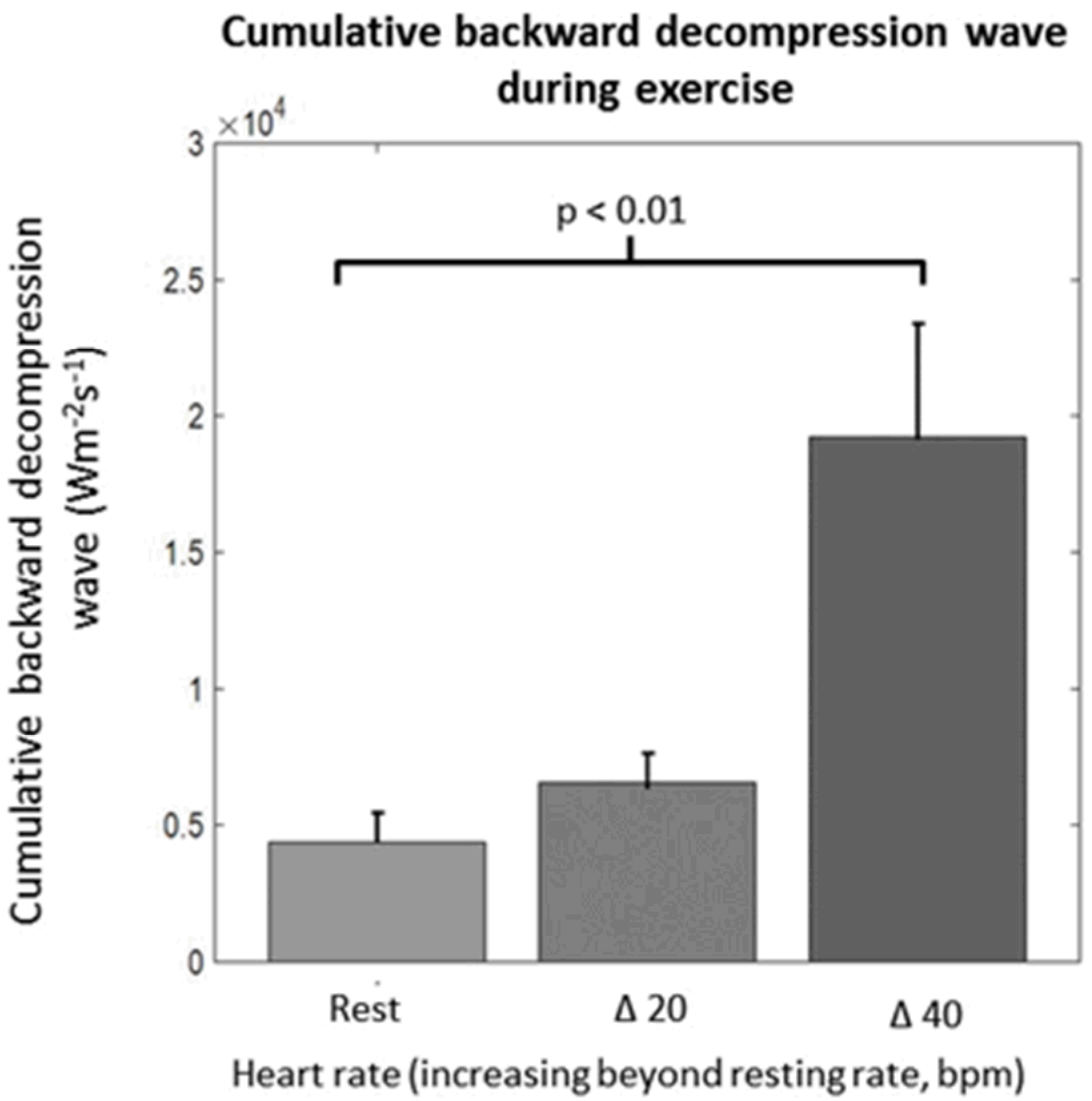
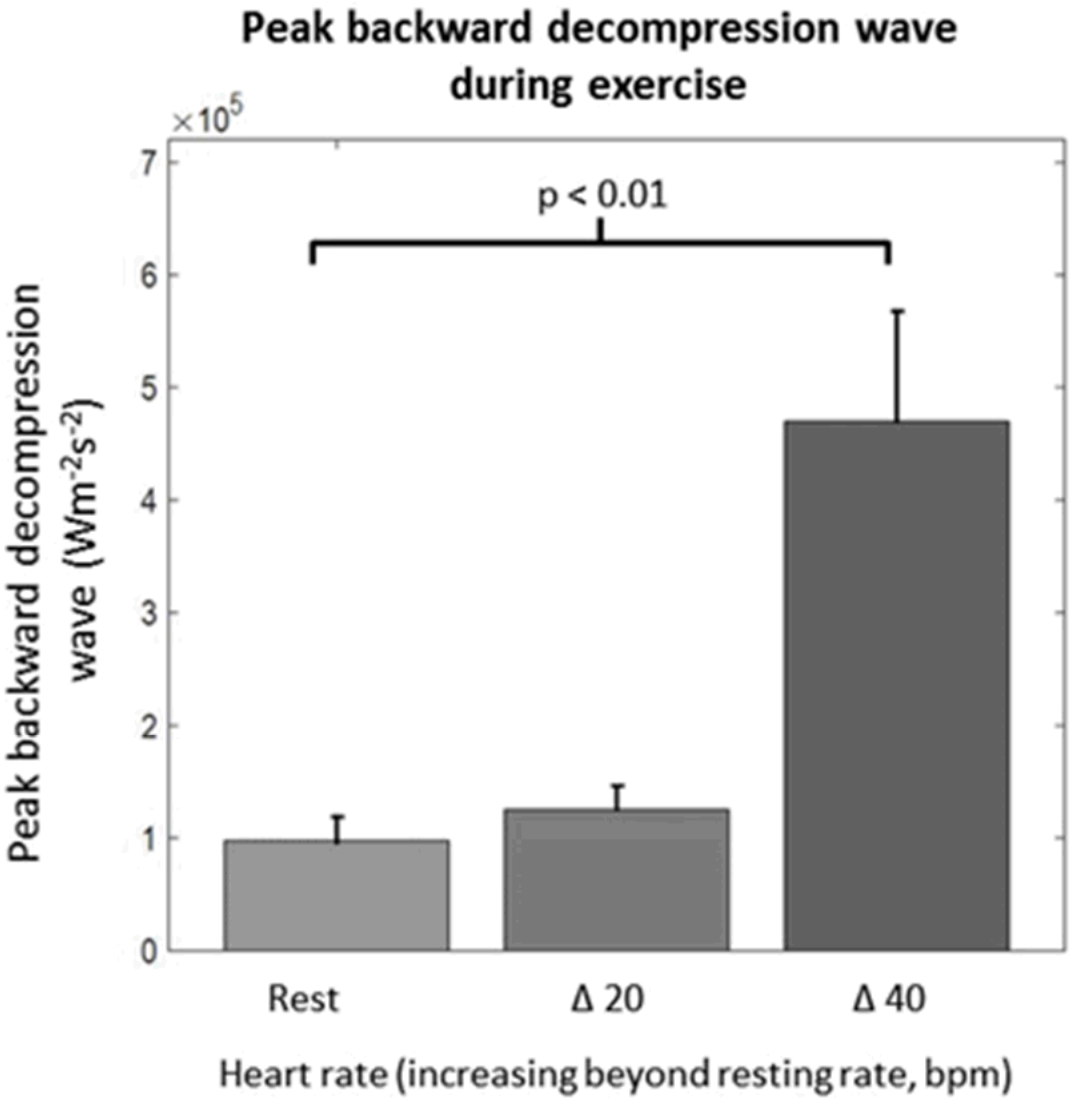
Filename: fig5.tif


Cumulative backward decompression wave during exercise
×10^4
3
2.5
2
1.5
1
0.5
0
p < 0.01
Cumulative backward decompression wave (Wm^-2s^-1)
Rest
Δ 20
Δ 40
Heart rate (increasing beyond resting rate, bpm)


Peak backward decompression wave during exercise
×10^5
7
6
5
4
3
2
1
0
p < 0.01
Peak backward decompression wave (Wm^-2s^-2)
Rest
Δ 20
Δ 40
Heart rate (increasing beyond resting rate, bpm)