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Manuscript Information

Journal name:	American journal of physiology. Heart and circulatory physiology
Manuscript #:	66664
Manuscript Title:	Estimation of coronary wave intensity analysis using non-invasive techniques and its application to exercise physiology.
Principal Investigators:	Alun D. Hughes (alun.hughes@ucl.ac.uk) J Davies (justindavies@heart123.com) Je Davies (justin.davies@imperial.ac.uk) Ss Nijjer (s.nijjer@yahoo.co.uk) S Sen (sayan.sen@imperial.ac.uk) Dp Francis (d.francis@imperial.ac.uk)
Submitter:	Alun D. Hughes (alun.hughes@ucl.ac.uk)

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1   **Estimation of coronary wave intensity analysis using non-invasive**

2   **techniques and its application to exercise physiology**

3   Christopher J. Broyd MBBS PhD*, Sukhjinder Nijjer MB ChB*, Sayan Sen MBBS PhD*, Ricardo

4   Petraco MD*, Siana Jones MSc BSc.‡, Rasha Al-Lamee MBBS*, Nicolas Foin PhD*, Mahmud

5   Al-Bustami MD[+], Amarjit Sethi MBBS PhD[+], Raffi Kaprielian MBBS MD[+], Punit Ramrakha

6   PhD[+], Masood Khan MB BChir, MA[+], Iqbal S Malik MBBS PhD[+], Darrel P. Francis MB BChir MA

7   MD*, Kim Parker PhD*, Alun D. Hughes PhD‡, Ghada W. Mikhail MBBS MD [+], Jamil Mayet

8   MB ChB MD*, Justin E. Davies MBBS PhD*.

9   *Imperial College London, +Imperial College London NHS Trust, ‡University College London

10

11   Running title: Broyd. Construction of non-invasive coronary WIA.

12   **Author for correspondence:**

13   Dr Christopher Broyd

14   The international centre for circulatory health

15   59-61 North Wharf Road

16   London

17   W21LA

18   c.broyd@imperial.ac.uk

19   Tel: +44 7859 072 797

20   Fax: +44 208 082 5109

21

22   Word count: 4174   References: 43   Figures: 5   Tables: 4

23   Subject codes: [125] Exercise testing, [29] coronary imaging, [31] echocardiography, [15]

24   hypertrophy, [33] other diagnostic testing

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 $-13.8\pm7.1\times10^4$ $Wm^{-2}s^{-2}$, concordance correlation coefficient (CCC) 0.73, p<0.01; cumulative -64.4 ± 32.8 vs $-59.4\pm34.2\times10^2$ $Wm^{-2}s^{-1}$, 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 $-47.0\pm29.5\times10^4 Wm^{-2}s^{-2}$ (p<0.01 vs rest) and cumulative BDW $-19.2\pm12.6\times10^3$ $Wm^{-2}s^{-1}$ (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

2

48 **Note and noteworthy**

49   Coronary wave-intensity analysis can be measured non-invasively potentially translating it from a

50   primary research tool to a clinical modality. Application to larger studies will permit exploration of its

51   potential predictor of outcome and facilitate examination of the effect of pharmacological (or other)

52   interventions on coronary wave-intensity in various sub-groups.

53

Introduction

54

55 Wave intensity analysis (WIA) provides a time-domain separation of up- and down-stream

56 wavefronts travelling at a single-point within a fluid medium and can elucidate the basis of temporal

57 blood flow velocity changes within the cardiovascular system. As the product of the first derivatives

58 of pressure (dP) and flow (dU) it is able to both qualify (in terms of direction) as well as quantify (in

59 terms of magnitude) energy transfer.

60 In humans it has been applied to many large arteries including the carotid and radial arteries(26, 43)

61 as well as the aorta(17), but has proven most useful in investigating the coronary circulation where

62 pressure gradients arising both proximally (aortic) and distally (myocardial) influence coronary

63 flow(7). The dominant wave driving coronary flow, the backward decompression wave (BDW),

64 originates distally from the myocardium at the onset of diastole and is generated by active

65 myocardial relaxation and resultant decompression of the intramyocardial microvasculature

66 producing a distal-to-proximal pressure gradient and thus a 'suction' effect. The backward

67 decompression wave is reduced in left ventricular hypertrophy(7), increased in severe aortic

68 stenosis(5), increases in response to pacing(40) or exercise(23) and can be used to predict

69 myocardial recovery after infarction(39).

70 Whilst many peripheral arteries are amenable to interrogation using non-invasive Doppler and

71 tonometric-based surrogates of pressure, until now the only way to perform coronary WIA is

72 invasively during angiography using intracoronary pressure- and flow-sensor tipped wires. However,

73 now it is possible to obtain acceptable surrogates of these measures non-invasively using

74 transthoracic Doppler ultrasound(34) and tonometry or cuff-based estimates of the central (aortic)

75 pressure waveform(16, 22, 24).

76 Therefore, we set out to perform a non-invasive measurement of coronary WIA using these

77 modalities in patients with normal coronary arteries. For further validation we assessed the

78   association of the magnitude of the backward decompression wave with two parameters that are

79   known to affect wave-intensity: exercise and left ventricular mass.

80

81

82   **Glossary**

83   c – wavespeed

84   CCC – Lin's correlation coefficient of concordance

85   CFR – Coronary Flow Reserve

86   ECG – ElectroCardioGram

87   iFR – instantaneous wave-free ratio

88   LAD – Left Anterior Descending artery

89   Pa – Proximal pressure

90   Pd – Distal pressure

91   PdPa – Pd to Pa ratio

92   PRF – Pulse Repetition Frequency

93   SD – Standard Deviation

94   WIA – Wave Intensity Analysis

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

96   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

121   laterally across the chest wall until the LAD was clearly in view with an angulation of less than 20° to

122   the probe. Pulse wave Doppler was applied with a sampling width of 7.5-10mm and multiple

123   coronary flow signals recorded. Data were exported as a high resolution image file. Simultaneously,

124   a suprasystolic waveform was recorded and calibrated with the brachial blood pressure using a cuff-

125   based device (Pulsecor, Auckland, New Zealand). The unprocessed data was exported as a Matlab

126   file. A full echocardiographic study was then undertaken including calculation of left ventricular

127   mass(19).

Data Processing

129   The central pressure waveform was estimated from the Pulsecor raw data using a modification of

130   the approach described by Lowe *et al*(24)*.* A minimum of two suprasystolic recordings were made;

131   anything less than 'good' quality data (as recognised by the Pulsecor system's quality-control) was

132   repeated. Each waveform was then aligned according to the peak negative dP/dt before ensemble-

133   averaging in order to prevent over-smoothing of the early diastolic section of the pressure waveform

134   which is essential for the construction of the backward decompression wave.

135   Non-invasive pressure and flow data were aligned using the "foot" of the pressure waveform and

136   the ECG-QRS from echocardiography (mean number of cardiac cycles 21±9). Invasive data were

137   aligned according to ECG-gating accounting for the inherent Combomap flow-pressure offset (mean

138   number of cardiac cycles 63±58).

139   After alignment and beat selection, both invasive and non-invasive data were processed using the

140   same automated Matlab software which involved an identical Savitsky-Golay filter (polynomial order

141   3, window size 51). The non-invasive data were analysed by an observer blinded to the invasive

142   analysis results.

143   Wave-intensity analysis

144   Wavespeed (c) was calculated using the single-point method(8). Wave-intensity analysis was

145   calculated as previously described(7). Briefly, we used the product of the first time derivatives of

146   pressure (dP/dt) and velocity (dU/dt) so the results are independent of the sampling frequency used.

147   The waves can be separated into proximally (WI_+) and distally (WI_-) originating waves as well as net

148   wave intensity using:

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

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

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

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

150   To separate coincident waves from proximal and distal origins the change in pressure was separated

151   into its wave components: dP_+/dt(proximal) and dP_-/dt(distal).

$$\frac{dP_+}{dt} = \frac{1}{2}\left(\frac{dP}{dt} + \rho c\left(\frac{dU}{dt}\right)\right)$$

$$\frac{dP_-}{dt} = \frac{1}{2}\left(\frac{dP}{dt} - \rho c\left(\frac{dU}{dt}\right)\right)$$

152   Cumulative wave intensity (i.e. wave energy) was calculated for each wave by measuring the area

153   under the peak of the wave intensity versus time curve. The cumulative intensity of each individual

154   wave was also calculated as a proportion of the total cumulative wave intensity over the cardiac

155   cycle (termed 'wave energy fraction').

156   **Non-invasive coronary wave intensity analysis in exercise**

157   A subgroup of 10 patients went on to have non-invasive coronary wave-intensity calculated during

158   exercise. Patients were selected on the basis of optimal coronary flow windows and the physical

159   ability to perform an exercise regimen reliably. They were asked to withhold any rate-limiting

160   pharmacological agents in the 48 hours prior to attendance and avoid alcohol, nicotine or nitrates in

161   the preceding 24 hours.

162   Patients were exercised during echocardiography using a semi-recumbent ergometer exercise bike

163   (Ergoline, Stuttgart, Germany). Patients were positioned according to their optimal

164   echocardiographic windows, typically semi-recumbent at 45 degrees and towards their left lateral

165   side. Coronary flow and central aortic pressure were recorded during graded exercise according to a

166   pre-determined standardised incremental exercise protocol(32) based on the patient's weight and

167   age, typically starting at 25W and increasing by 20W each minute. Data was acquired when the heart

168   rate was 20 and 40bpm above resting following cessation of exercise. To preserve an optimal

169   pressure signal, an assistant held the patients arm static following exercise whilst Pulsecor data was

170   simultaneously acquired.

171 **Reproducibility**

172 For each patient, haemodynamic data was recorded before and after the conventional

173 echocardiographic study. The reproducibility of hemodynamic measurements was calculated by

174 examining separate 30-s non-invasive recordings of blood pressure, velocity and wave intensity for

175 each patient.

176 **Statistics**

177 The data was analysed using STATA 11 and Matlab R2015a. Continuous variables are reported as

178 mean ± standard deviation (SD). The Bland-Altman method was used to quantify agreement

179 between non-invasive and invasive wave-intensity and to analyse reproducibility data. Lin's

180 correlation coefficient was used to express concordance (CCC), and the coefficient of variation (CV)

181 was calculated for reproducibility data as the ratio of the standard deviation of difference between

182 measures to the mean value of the measure. 2-dimensionsal cross-correlation coefficients were

183 used as a measure of similarity between non-invasive and invasive waveforms. Invasive and non-

184 invasive values were compared using a Wilcoxon matched-pairs signed-ranks test. Exercise

185 haemodynamic data was analysed using Cuzick's test for trend. Correlation was assessed with

186 Pearson's correlation coefficient. Fisher's r-to-z transformation was used to compare correlation

187 coefficients. A p value of less than 0.05 was deemed significant.

188

189 **Results**

190 **Patient Characteristics**

191 Of the 28 patients recruited, 23 had appropriate echocardiographic windows to allow coronary flow

192 analysis. In one patient it was impossible to obtain an adequate invasive Doppler signal for analysis.

193 The remaining 22 patients make up the study population. Mean age was 60 ± 12 (14 male). Systolic

194 function was preserved (mean ejection fraction 59%) with no significant valvular disorders. Risk

195 factors for coronary disease included hypercholesterolaemia (58%), hypertension (35%), diabetes

196 (6%) and smoking (6%) (Table 1). Echocardiographic data are displayed in Table 2.

197 **Haemodynamic data**

198 Maximum coronary flow velocities were similar in the invasive and non-invasive groups but

199 minimum velocity was higher by non-invasive methods (Table 3). Invasive systolic and mean

200 pressure was higher by invasive methods, although diastolic pressure did not differ (Table 3). Mean

201 cross-correlation coefficients between invasively measured Pa (aorta - catheter tip) and Pd (coronary

202 wire pressure) were 0.99±0.00. Mean resting Pd/Pa was 1.0 ± 0.03 and iFR 0.99 ± 0.03. The minimum

203 dP/dt was higher invasively than non-invasively (-0.57±0.21 vs. -0.36±0.16 mmHg.s-1; p<0.01) but

204 with a favourable concordance (CCC=0.44, p<0.01); additionally the mean cross-correlation

205 coefficient between invasive and non-invasive pressure waveforms was very high (r = 0.99±0.01).

206 The time of minimum dP/dt from the foot of the systolic aortic upstroke was 305ms invasively and

207 281ms non-invasively (p = 0.02).

208 As previously described, 6 different waves were identified in the cardiac cycle. Each wave was

209 characterized by origin and direction of travel (forward-traveling waves originating proximally and

210 backward-traveling waves originating distally), character (compression or decompression), and

211 effect on coronary blood flow velocity (acceleration or deceleration waves)(7). Focus was given to

11

212   the forward compression wave, forward decompression wave and backward decompression wave as

213   the waves of most physiological importance (Figure 1).

214   Peak backward decompression wave was $-14.9 \pm 7.8 \times 10^4$ $Wm^{-2}s^{-2}$ invasively and $-13.8 \pm 7.1 \times 10^4$

215     $Wm^{-2}s^{-2}$ non-invasively and measures showed good concordance (CCC 0.73, $p<0.01$). Cumulative

216   wave intensity was $-64.4 \pm 32.8 \times 10^2$ $Wm^{-2}s^{-1}$ invasively compared to $-59.4 \pm 34.2 \times 10^2$ $Wm^{-2}s^{-1}$ non-

217   invasively (CCC 0.66, $p<0.01$) (Figure 2, Table 3).

218   The non-invasive measures of other waves underestimated their magnitude compared with invasive

219   measures (Table 3). This meant the fraction backward decompression wave intensity was higher in

220   the non-invasive group (29.7±9.5% non-invasively vs 22.1±5.4% invasively, $p<0.01$) but there was a

221   correlation between the two techniques ($r = 0.45$, $p=0.04$). Wave speed was also lower by non-

222   invasive methods (Table 3). As previously reported[4], a correlation was also seen between the non-

223   invasive forward compression wave and the backward decompression wave ($r=-0.44$, $p=0.04$), this

224   was almost identical to that seen invasively ($r=-0.44$, $p=0.04$; Fisher's z=0, $p>0.99$).

225   Reproducibility

226   The mean±SD of the difference between the separate 30-s recordings of blood pressure was

227   2.2±2.0mmHg (CV= 2.4%). The mean±SD of the difference between the separate 30-s recordings of

228   flow velocity was 0.7 ± 0.7 cms^{-1} (CV = 2.0%). The mean±SD of the difference between the separate

229   30-s recordings of the cumulative backward decompression wave was $-1.6 \pm 2.3 \times 10^2$ $Wm^{-2}s^{-1}$ (CV =

230   2.0%). The mean±SD of the difference between the separate 30-s recordings of the peak backward

231   decompression wave was $-0.8 \pm 0.8 \times 10^{-4}$ $Wm^{-2}s^{-2}$ (CV = 4.4%).

232   Left Ventricular mass

233   Mean left ventricular mass was 163±37g with 5 patients meeting the definition of left ventricular

234   hypertrophy[19]. There was a significant negative correlation between left ventricular mass and both

235   non-invasive ($r=-0.48$, $p=0.02$, Figure 3) and invasive ($r=-0.49$, $p=0.01$) backward decompression

236   wave fraction. No significant difference was found between the two correlation coefficients (z =

237   0.21, p=0.83). There was also a significant positive correlation between left ventricular mass and the

238   non-invasive forward compression wave fraction (r=0.50, p=0.02). No other correlations were noted

239   between mass and any of the other waves or their fractional energy.

240   **Exercise wave intensity**

241   One patient was excluded from this sub analysis because of technically-inadequate coronary flow

242   sampling during exertion. Peak coronary flow rose during exercise from 23.2±8.2 cm/s to 42.2±17.8

243   cm/s (p<0.01 for trend) as did systolic pressure (120±13.0 to 140±23.4 mmHg, p=0.07 for trend).

244   Diastolic pressure rose only modestly from 82.3±10.5 to 85.9±11.0mmHg (p=0.68 for trend).

245   Both peak and cumulative backward decompression wave demonstrated a progressive increase with

246   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

247   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 -

248   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

249   10^3 $Wm^{-2}s^{-1}$ at peak (z=-3.80, p<0.01 for trend) (Figure 4 & 5, Table 4).

250

251

Discussion

253 We have demonstrated that the coronary wave intensity profile can be measured with reasonable

254 fidelity non-invasively using Doppler echocardiography and the central blood pressure waveform

255 estimated from a brachial blood pressure cuff device. The agreement between wave intensity

256 measured invasively and non-invasively was good, the correlation between the backward

257 decompression wave and LV mass was similar between invasive and non-invasive methods, and

258 exercise induced a graded increase in the backward decompression wave intensity demonstrating

259 the sensitivity of this non-invasive method to a physiological intervention.

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

261 With the introduction of newer echocardiography machines with 2nd harmonic imaging and high

262 frequency transducers, it has become possible to obtain a very accurate coronary flow envelope that

263 shows equivalence with invasively derived measures(14, 34, 35). This technique is now able to

264 calculate coronary flow reserve (CFR) and has been used to predict outcome in a variety of disease

265 states(2, 3, 33).

266 Previous work has sought to use single, resting measures of coronary flow alone in order to assess

267 microvascular dysfunction with varying degrees of success. To that end, correlates have been

268 recognised between invasively measured systolic flow reversal(41), diastolic deceleration time(15,

269 20) and recovery after myocardial infarction and these markers have been adopted non-invasively as

270 well(29). Combining non-invasive pressure and flow data to calculate coronary wave intensity offers

271 a potentially valuable index of coronary haemodynamics.

272 The derivation of wave-intensity from pressure and flow tracings has previously been successfully

273 performed non-invasively in carotid(1, 28), brachial and radial arteries(43). This has resulted in a

274 large increase in its applicability providing insights into its relationship to outcomes(25) and the

275 differential effect of therapies(26). We have now shown that is also possible to measure wave

276   intensity in the left anterior descending artery using non-invasive measures of central pressure and

277   coronary flow. With this approach the backward decompression wave is equivalent to that seen in

278   previous invasive studies(7).

279   Our approach was focused on the three most clinically relevant waves within the cardiovascular

280   system, particularly the backward decompression wave as this provides insights regarding the

281   microcirculatory drive to coronary flow(5, 7, 11, 18). This wave has the largest magnitude and

282   therefore least potential for signal-to-noise errors. Additionally, we used the peak negative dP/dt of

283   the pressure waveform for alignment prior to ensembling and optimised the Doppler envelope for

284   this portion of the cardiac cycle. These factors may explain firstly why our measure of the backward

285   decompression wave was most accurate but also, in part, why the other waves were underestimated

286   since co-registration errors in the ensemble will tend to increase with distance from the fiducial

287   point. Nevertheless, a strong correlation between the forward compression wave and backward

288   decompression wave was seen as has been recognised invasively(7) implying an adequate

289   approximation over the whole cycle.

290   To test the validity of our measure of the backward decompression wave further, we examined it

291   under variable physiological and pathological environments and assessed whether it performed

292   similarly to reported invasive measures.

Left Ventricular Mass

294   Increased LV mass is associated with adverse cardiovascular outcomes(12, 21). CFR is reduced with

295   left ventricular hypertrophy(13), a feature which is reversible with therapy(27) so that despite an

296   increased muscle mass, the ability of the heart to regulate its own blood supply is attenuated in left

297   ventricular hypertrophy which reflects an inefficiency of myocardial function.

298   WIA can also provide an insight into this myocardial efficiency and can demonstrate the interplay

299   between myocardial structure and coronary flow despite similar coronary flow velocity rates(42).

300   Invasive studies have shown that left ventricular hypertrophy results in a reduction in the backward

301   decompression wave energy fraction(7). As such, coronary wave-intensity may be able to provide

302   prognostic information in a similar fashion to CFR and a technique, such as this one, to increase its

303   potential applicability would therefore be useful. In the present study we have confirmed the

304   relationship between invasively assessed backward decompression wave energy fraction and left

305   ventricular mass and gone on to show this relationship is detected using our non-invasive method

306   for measuring coronary wave intensity with acceptable accuracy.

307   Whilst only 5 patients from our cohort met a definition of left ventricular hypertrophy, the effect of

308   left ventricular mass on both coronary physiology(27) and mortality(12) is continuous as is wave-

309   intensity analysis. We would therefore anticipate a correlation between left ventricular mass and

310   wave-intensity even when LV mass is within the 'normal' range and this is indeed what we found.

Exercise Physiology

312   At rest, haemoglobin concentration and oxygen extraction of coronary flow are already at 70-80%

313   maximum capacity and therefore the resultant 5-fold increase in the oxygen requirements of the

314   myocardium during exercise is largely served by an increase in coronary blood flow. Accordingly,

315   peak values of coronary blood flow in dynamic exercise are 3-5 times the resting level(10), an

316   increase that is influenced by the interaction between the relaxing myocardium and decompression

317   of small intra-myocardial blood vessels which can be quantified using the backward decompression

318   wave. This has been described in animal models(40) and in humans(6, 23). We therefore sought to

319   demonstrate an appropriate response in non-invasive wave intensity with exercise.

320   We found that coronary wave-intensity can be assessed in most patients at moderate levels of

321   exertion; in a proportion of patients, it can even be gauged at more intense levels. With exercise,

322   there is an appropriate progressive increase in the magnitude of the backward decompression wave.

323   This reflects the increased 'suction' effect of the myocardium on the coronary circulation with

324   increasing oxygen demand. In turn, this results in a measurable increase in coronary flow rate and

325   blood supply.   Peak and cumulative backward decompression wave intensity were increased 3-4

326   fold during exercise, which is similar in magnitude to that reported in other studies(5, 23).

327   **Applications**

328   The use of this technique has a wide variety of applications in disease states. With moderate

329   expertise, it can be measured in the majority of patients, carries no risk and requires no

330   pharmacological agents. Therefore, its key feature is in its ability to perform serial measurements in

331   the interrogation of patients who have insufficient clinical indication to undergo angiography, or for

332   follow-up in those whom have had invasive assessment.

333   Previous work has demonstrated that patients with aortic stenosis have a strikingly abnormal wave-

334   intensity profile that normalises immediately following valve implantation(5). Using non-invasively

335   derived measures of wave intensity may permit a further measure of myocardial burden to be

336   estimated in patients with mild or moderate aortic stenosis and thus aid the timing of intervention.

337   Similarly, in patients with other cardiomyopathies where non-invasively derived CFR can predict

338   outcome(3, 33) this marker may allow further risk stratification and monitoring of the effect of

339   therapy.

340   Given that non-invasively measured wave intensity is able to recognise subtle resting abnormalities

341   in myocardial function it is also possible that it may have potential as a pre-clinical screening tool in

342   patients with risk factors for cardiovascular disease. In those at risk with an abnormal resting wave-

343   intensity profile, treatment could be instigated early and followed to ensure normalisation.

344   The ability to apply this technique to patients undergoing exercise opens further avenues to assess

345   disease states during exertion. In particular, valve disorders or progressive cardiomyopathic

346   conditions could be serially assessed during exercise to allow timing of intervention. In patients

347   unable to exercise, a pharmacological stressor could be applied to provide similar results. The

348   majority of the technical difficulties in measuring non-invasive exercise coronary wave-intensity

349   were actually due to the movement of the body whilst pedalling particularly at higher levels of

350   exertion. Therefore, with use of handgrip isometric exercise, it may possible to make this assessment

351   easier and given the sensitivity of wave-intensity analysis, only a moderate heart rate increase may

352   be required.

353   ## Disadvantages and Limitations

354   In this study, the measurement of non-invasive WIA was not performed exactly at the same time as

355   the invasive assessment but rather was undertaken serially within 30 minutes of the procedure.

356   However, patients remained supine between these two recordings and there was no marked change

357   in heart rate, coronary flow rate or pharmacological state of the patient and they remained supine

358   on the bed.

359   We assumed aortic pressure would be an acceptable surrogate of the LAD pressure waveform. This

360   assumption is the basis of pressure-based assessment of moderate coronary lesions(31, 38) and we

361   demonstrated similar waveform shapes of non-invasive central and invasive aortic and coronary

362   pressure using cross-correlation coefficients. However, recent data(4, 30) have suggested a

363   systematic error in central pressure estimation due to the Pulsecor's calibration using brachial

364   pressures, and similar biases have been reported for other non-invasive devices(9). It has been

365   suggested that calibration to mean and diastolic pressure may minimize this bias(4) and this issue

366   should be addressed in future studies. Whilst wave intensity employs the derivatives of the pressure

367   and flow waveforms so the impact of a BP calibration error on estimated wave intensity is likely to

368   be modest, consistent with this we found that minimum dP/dt, peak and cumulative wave intensity

369   estimated non-invasively was lower than invasive measures. For the BDW the resultant difference in

370   wave intensity were small (~10%) but for other more minor waves the differences were larger. The

371   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,

396   relative changes in this value would remain clinically relevant. Additionally, the backward

397   decompression wave has consistently shown itself to be the most clinically relevant wave(6, 7, 18,

398   23, 39).

Conclusion

400   It is possible to measure coronary wave intensity in the left anterior descending artery using widely

401   available non-invasive technology. This method provides an acceptably accurate assessment of the

402   backward decompression wave under resting conditions. The technique has sufficient sensitivity to

403   detect changes associated with left ventricular hypertrophy and exercise. It enhances the

404   applicability of coronary wave intensity to larger cohort-based studies where invasive pressure and

405   flow would be unethical or unpractical to obtain to provide greater understanding of myocardial-

406   coronary interaction. It also provides an opportunity to conveniently and safely make repeated

407   measurements following a range of pharmacological (and other) interventions.

408 **Funding Sources**

414

415 **Disclosures**

416 The authors report no disclosures.

417

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578 **Tables**

579 Table 1. Baseline patient demographics of 22 patients undergoing combined invasive and non-

580 invasive LAD wave-intensity analysis

581 Table 2. Baseline echocardiographic data of 22 patients undergoing combined invasive and non-

582 invasive LAD wave-intensity analysis.

583 Table 3. Invasive versus non-invasive coronary haemodynamics.

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

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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)

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

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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

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

602 Values are mean ± SD.

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		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

609 **Table 3. Invasive versus non-invasive coronary haemodynamics.**

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

611 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

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

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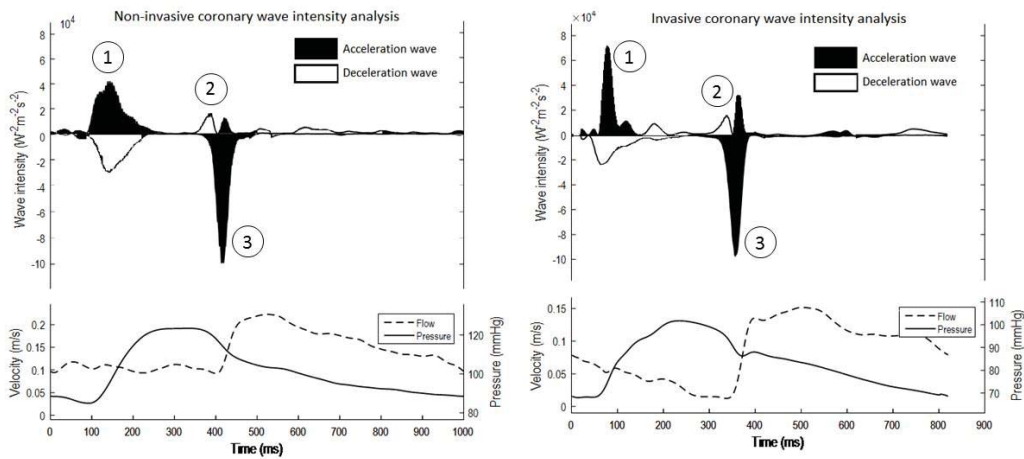
Figure 1. Invasive versus non-invasive wave intensity analysis. 6 waves were identified through both modalities.

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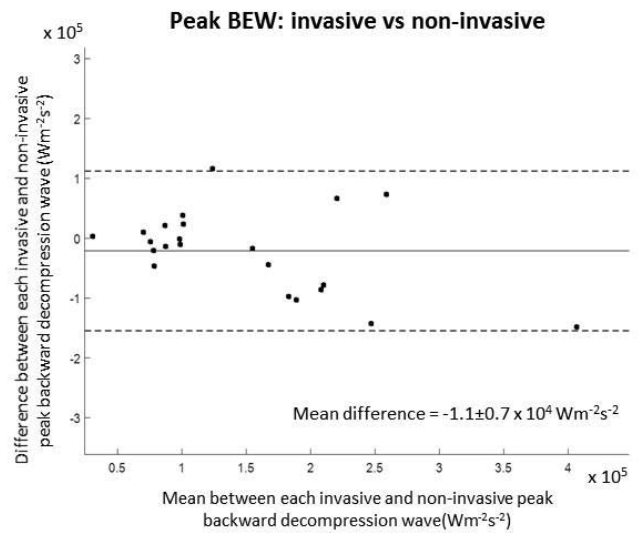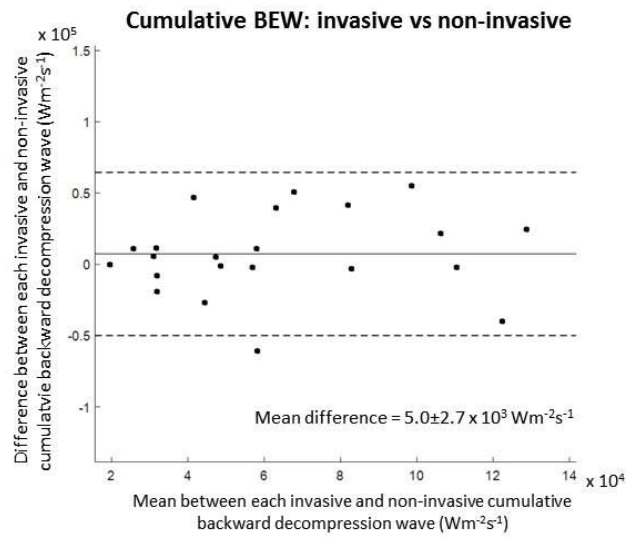
Figure 2. Bland Altman plot of invasive versus non-invasive backward decompression wave: peak (left) and cumulative (right),

Solid horizontal line represents mean difference and dashed lines the limit of agreement (±1.96x SD).
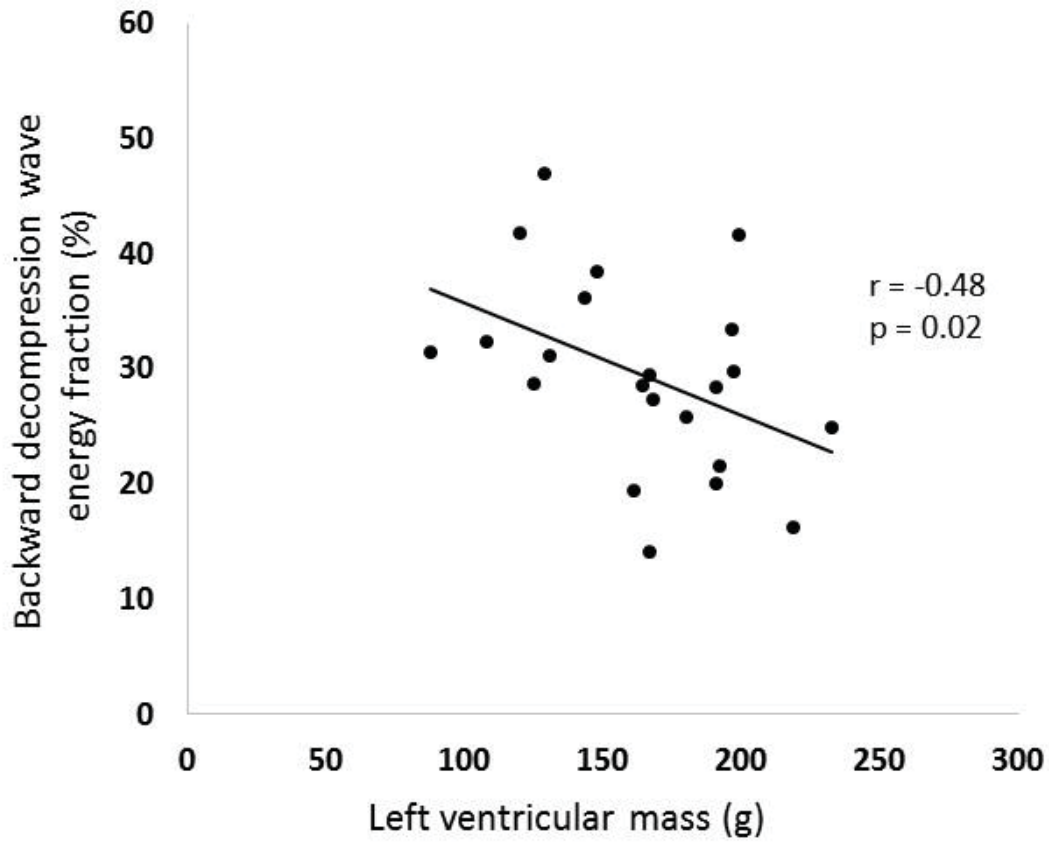
Figure 3. Scatterplot showing the relationship between the non-invasive backward decompression wave energy fraction and left ventricular mass.

The solid line represents the regression line and Pearson's correlation coefficient is shown.
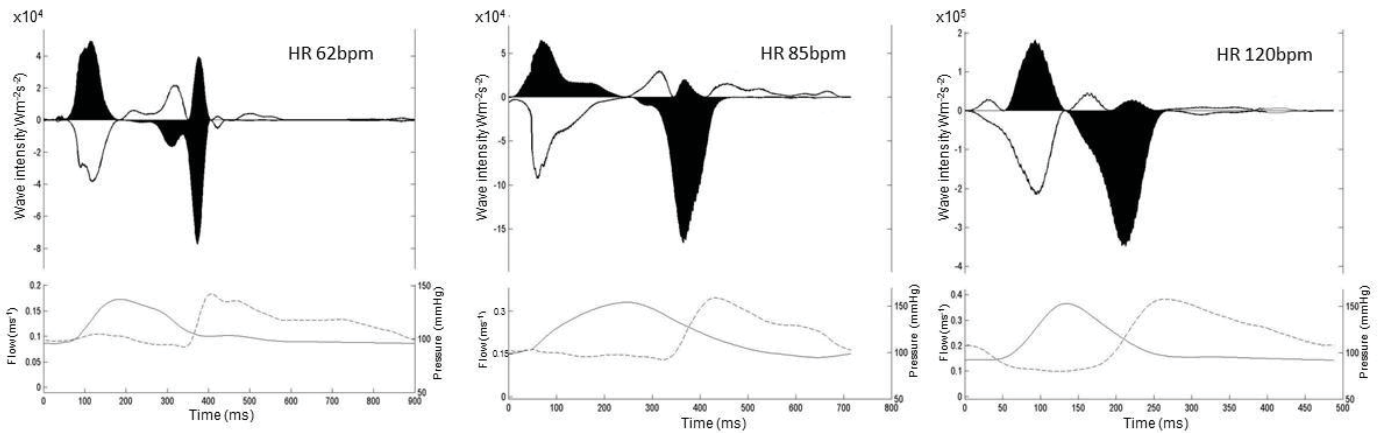
Figure 4. Coronary flow assessment and non-invasive wave-intensity analysis at increasing heart rates.

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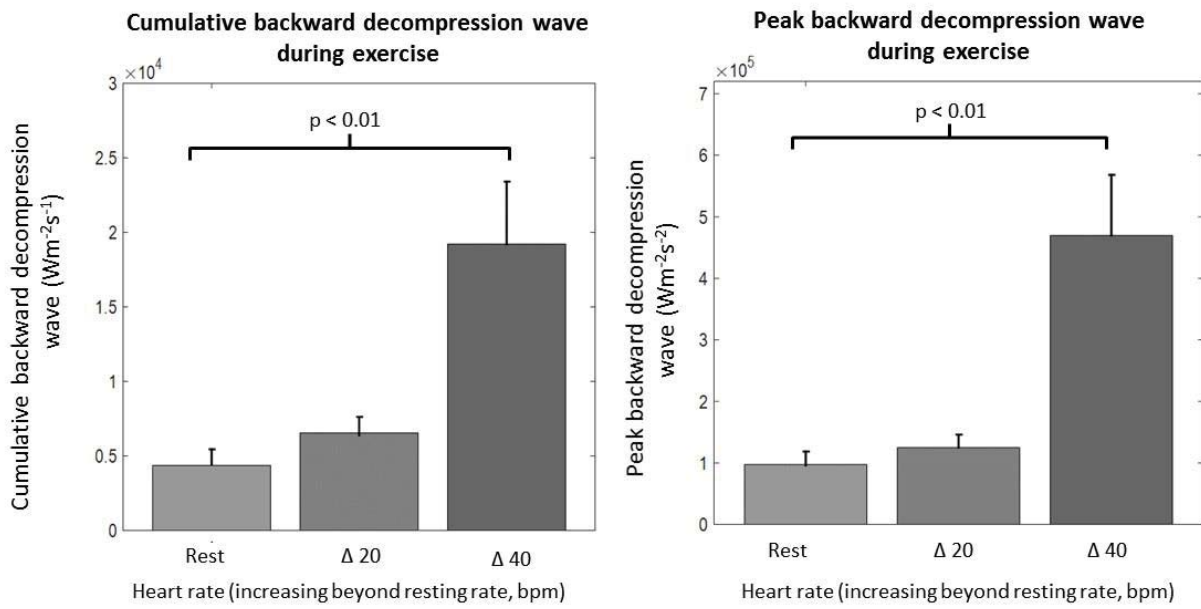
Figure 5. Peak and cumulative backward decompression wave with exercise.

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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Label: 1
Filename: fig1.tif
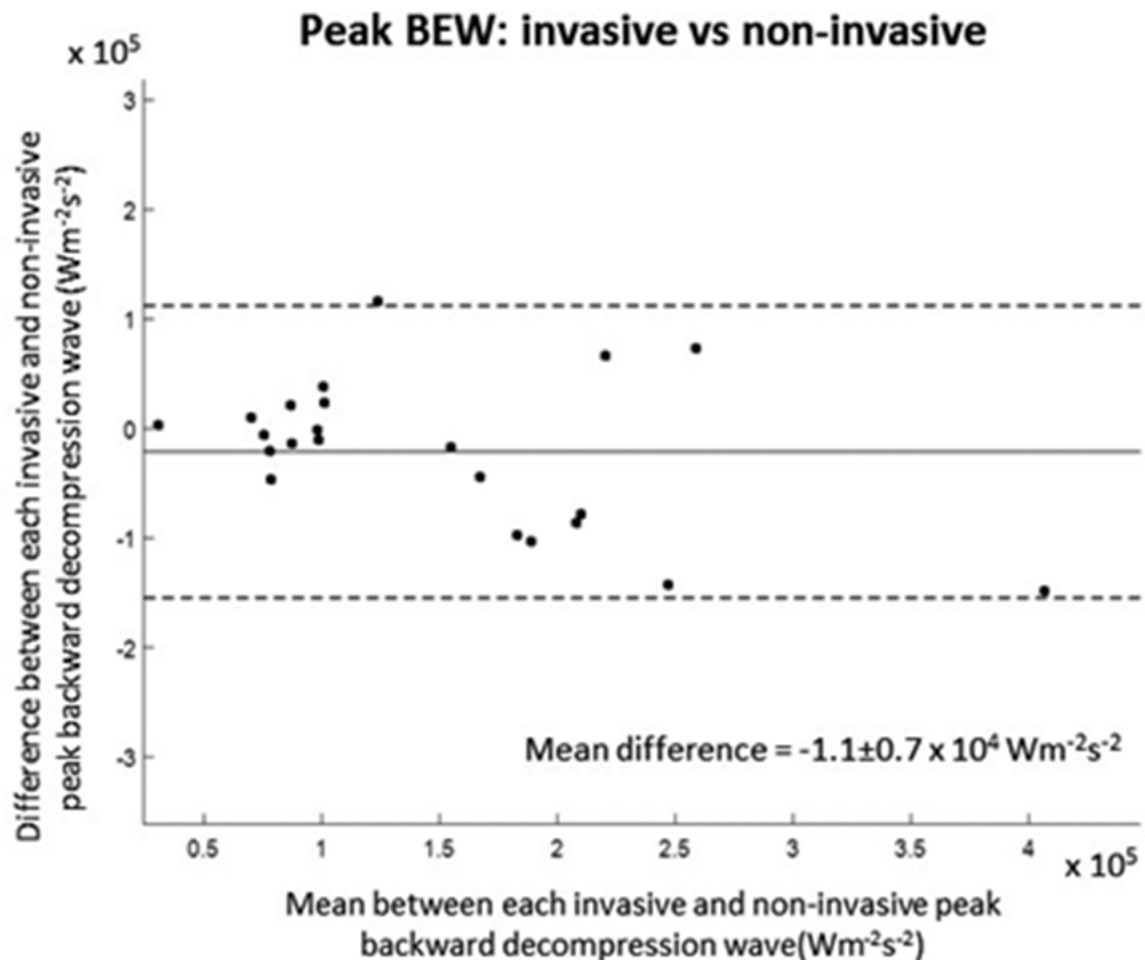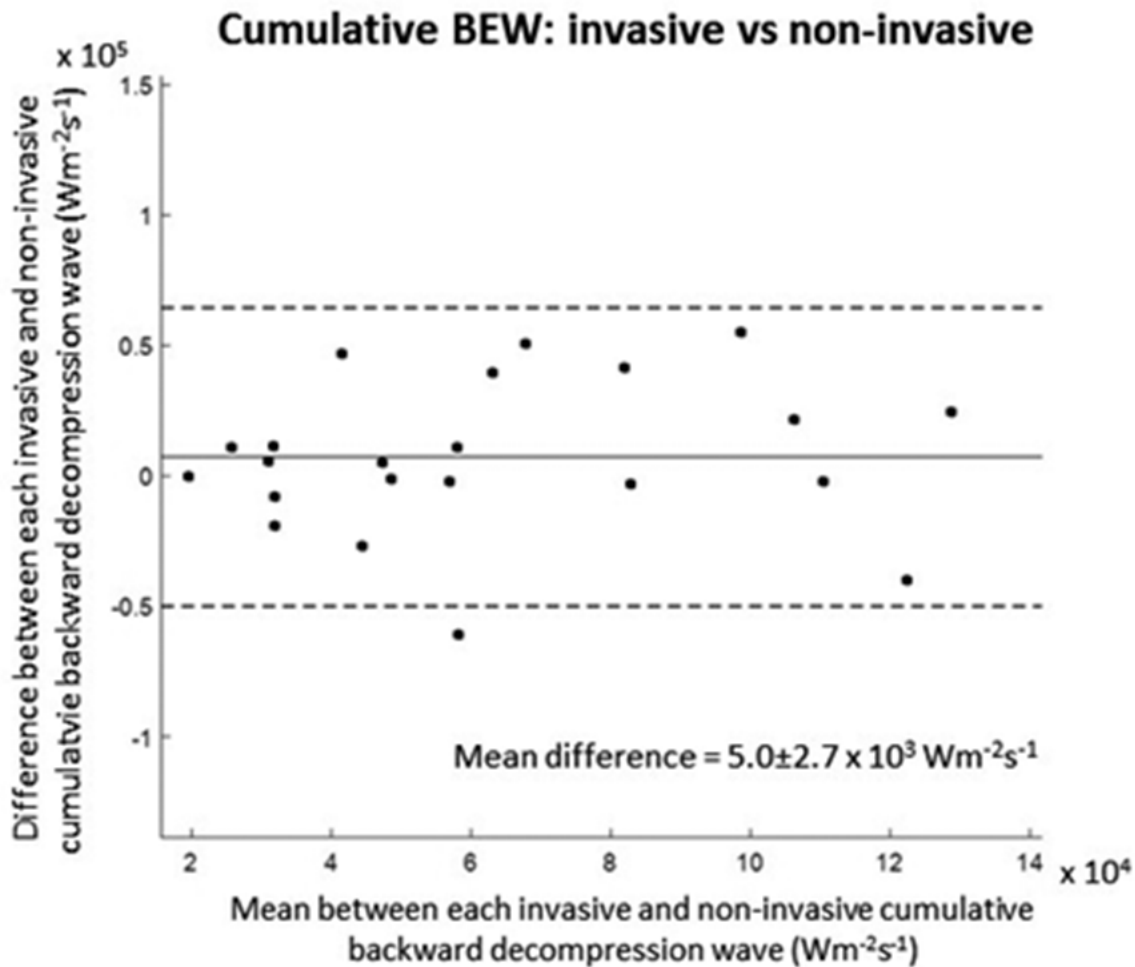
Non-invasive coronary wave intensity analysis
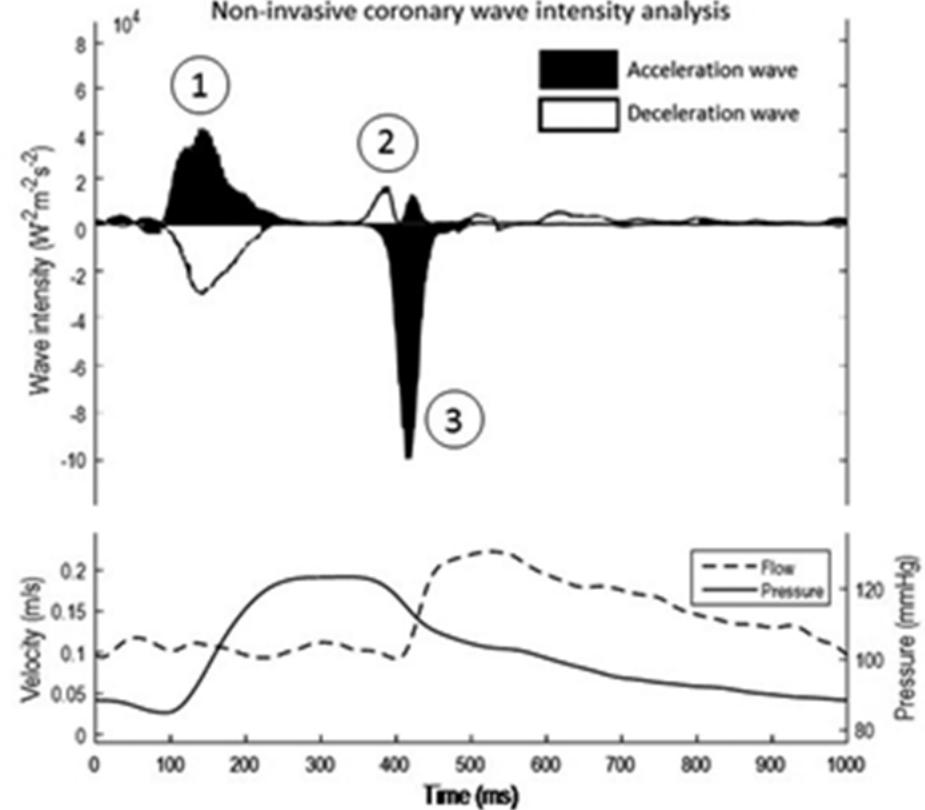
Invasive coronary wave intensity analysis
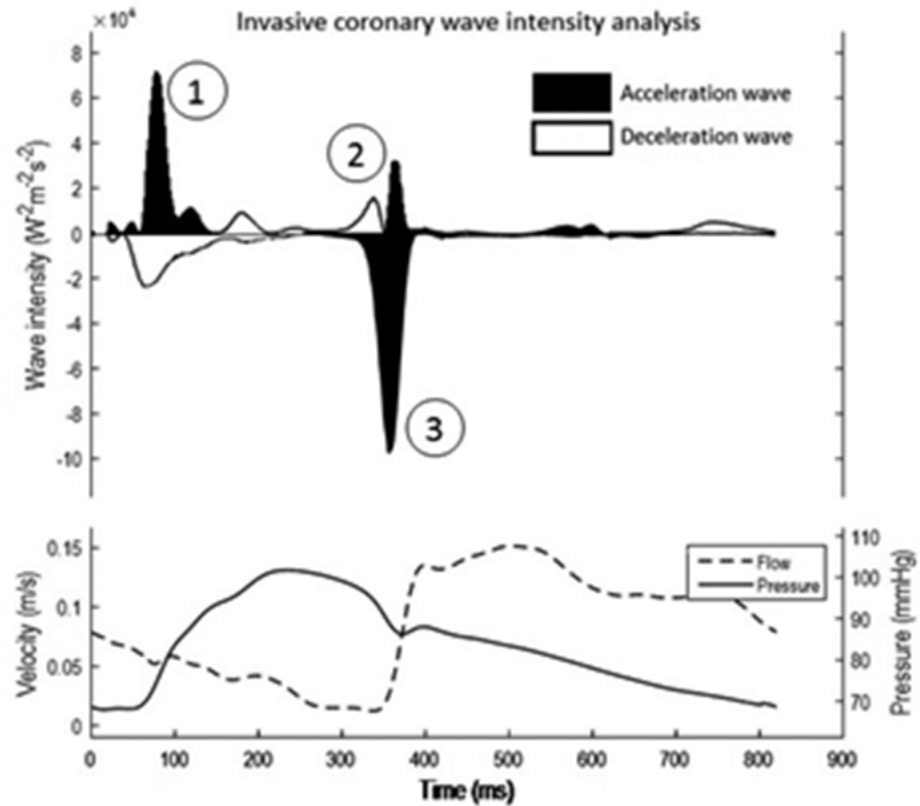
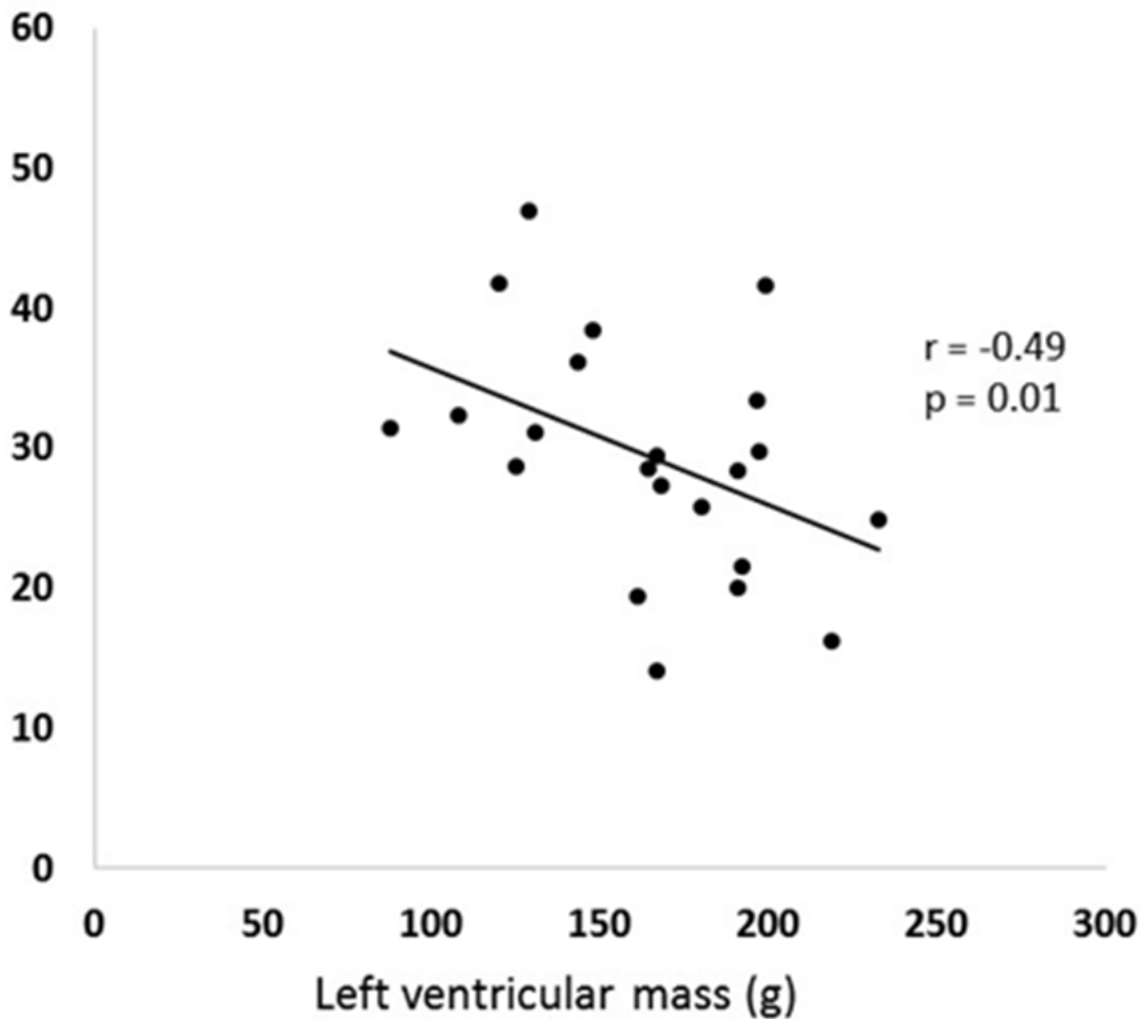Type of file: figure

Label: 2

Filename: Fig2.tif

Cumulative BEW: invasive vs non-invasive

Mean difference = 5.0±2.7 x 10³ Wm⁻²s⁻¹

Peak BEW: invasive vs non-invasive

Mean difference = -1.1±0.7 x 10⁴ Wm⁻²s⁻²

Type of file: figure
Label: 3
Filename: Fig3.tif

r = -0.49
p = 0.01

Type of file: figure

Label: 4

Filename: fig4.tif
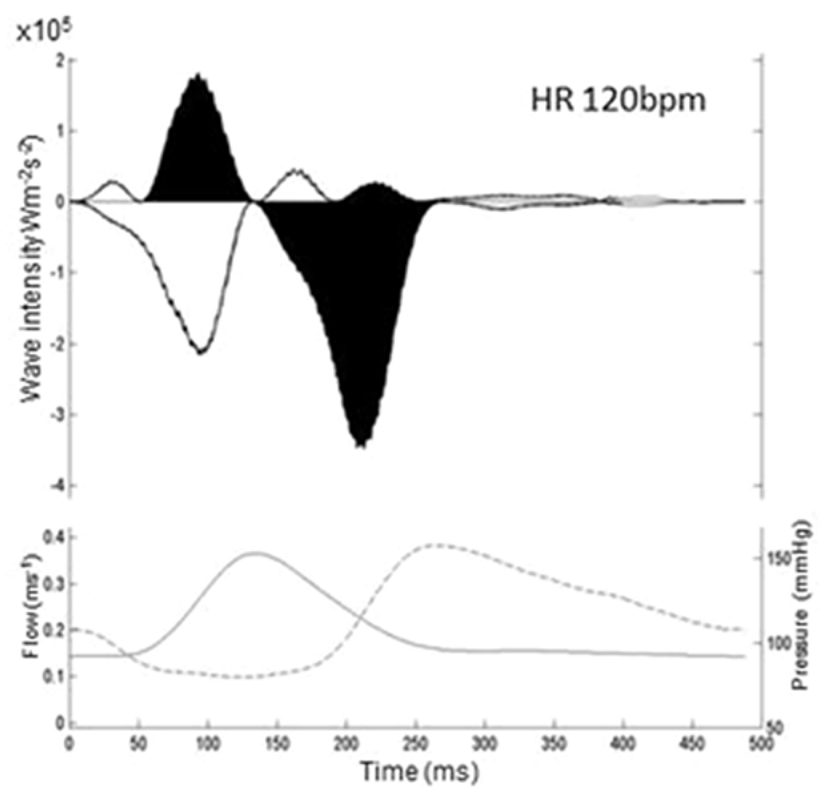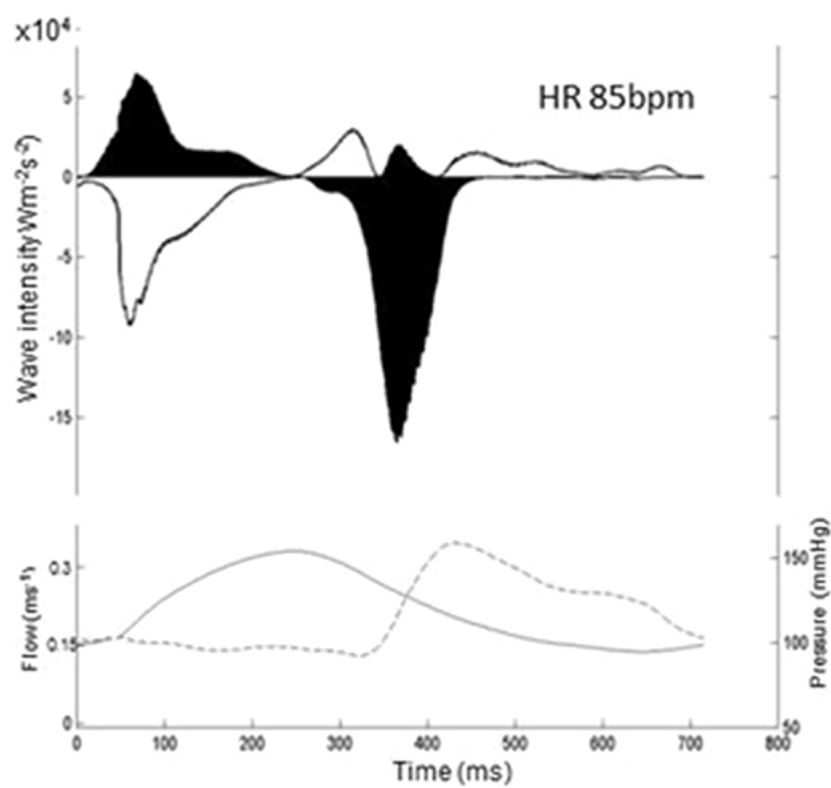
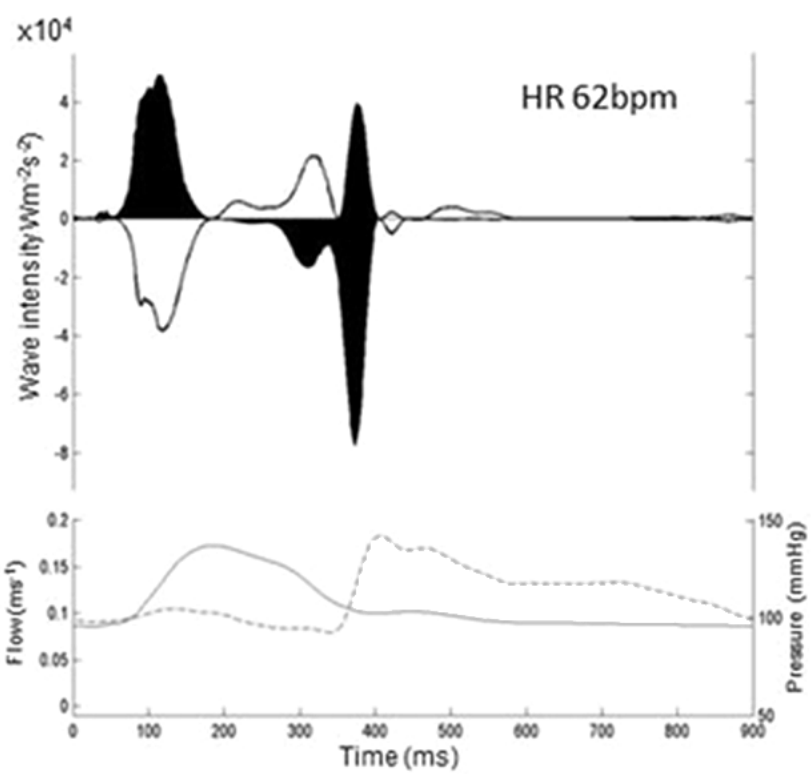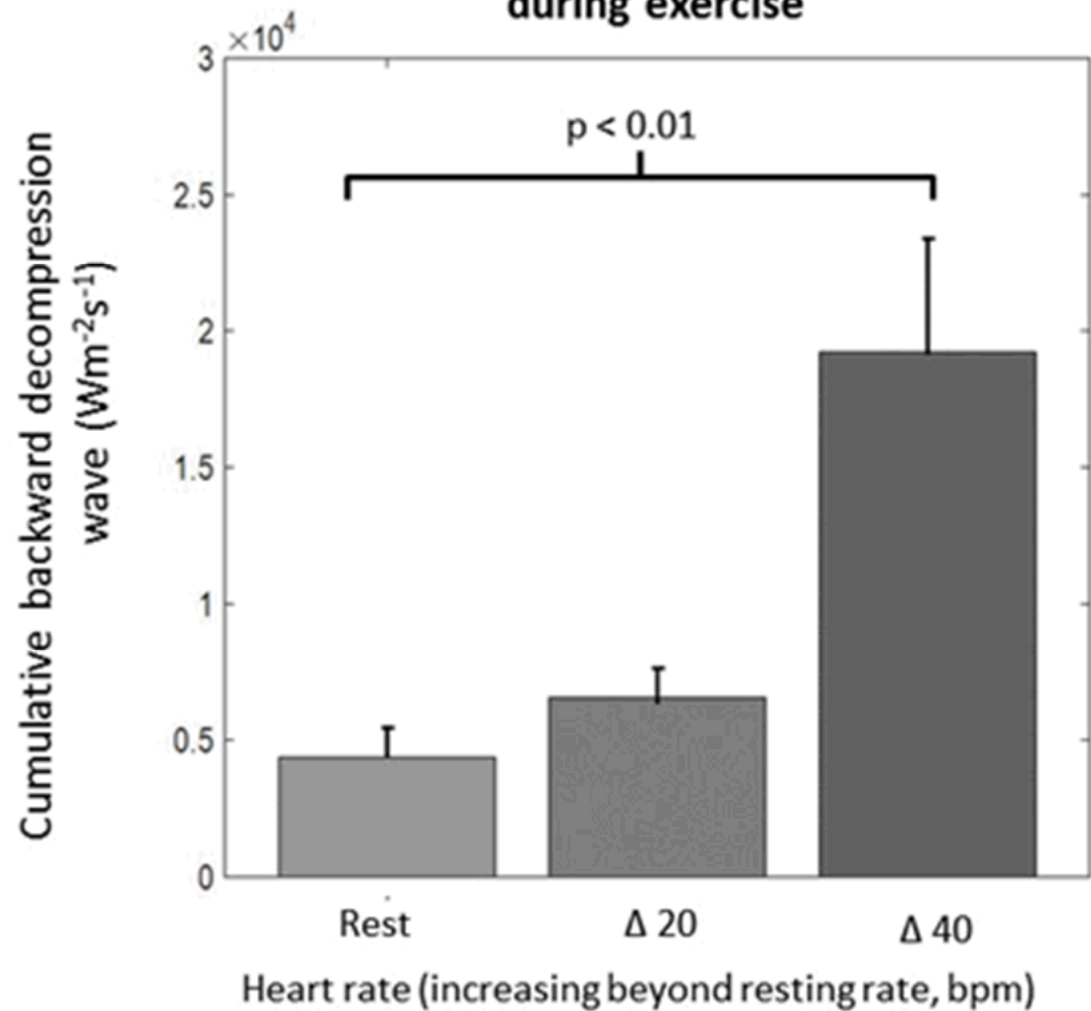Type of file: figure

Label: 5

Filename: fig5.tif

Cumulative backward decompression wave during exercise

x-axis: Heart rate (increasing beyond resting rate, bpm) — Rest, Δ 20, Δ 40

y-axis: Cumulative backward decompression wave ($Wm^{-2}s^{-1}$), $\times 10^4$

$p < 0.01$

Peak backward decompression wave during exercise

x-axis: Heart rate (increasing beyond resting rate, bpm) — Rest, Δ 20, Δ 40

y-axis: Peak backward decompression wave ($Wm^{-2}s^{-2}$), $\times 10^5$

$p < 0.01$