Cardiac-coronary interactions in humans: Mechanistic insights from wave intensity analysis
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Citation for published version (APA):
Rolandi, M. C. (2014). Cardiac-coronary interactions in humans: Mechanistic insights from wave intensity analysis

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Download date: 06 Dec 2018
Chapter 5

Synergistic Adaptations to Exercise in the Systemic and Coronary Circulations that Underlie the Warm-Up Angina Phenomenon

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Published in Circulation, 2012
ABSTRACT

The mechanisms of reduced angina on second exertion in patients with coronary arterial disease, also known as the warm-up angina phenomenon, are poorly understood. Adaptations within the coronary and systemic circulations have been suggested but never demonstrated \textit{in vivo}. In this study we measured central and coronary hemodynamics during serial exercise. 16 patients (15 male, 61±4 yrs) with a positive exercise ECG and exertional angina completed the protocol. During cardiac catheterization via radial access they performed 2 consecutive exertions (Ex1, Ex2) using a supine cycle ergometer. Throughout exertions, distal coronary pressure and flow velocity were recorded in the culprit vessel using a dual sensor wire whilst central aortic pressure was recorded using a second wire. Patients achieved a similar workload in Ex2 but with less ischemia than in Ex1 (p<0.01). A 33% decline in aortic pressure augmentation in Ex2 (p<0.0001) coincided with a reduction in tension time index (TTI), a major determinant of LV afterload (p<0.001). Coronary stenosis resistance was unchanged. A sustained reduction in coronary microvascular resistance resulted in augmented coronary flow velocity on second exertion (both p<0.001). These changes were accompanied by a 21% increase in the energy of the early diastolic coronary backward-travelling expansion, or suction, wave on second exercise (p<0.05), indicating improved microvascular conductance and enhanced LV relaxation. On repeat exercise in patients with effort angina, synergistic changes in the systemic and coronary circulations combine to improve vascular-ventricular coupling and enhance myocardial perfusion, thereby potentially contributing to the warm-up angina phenomenon.
INTRODUCTION

The variable relation between exercise and angina has been recognized for more than 200 years [1]. The terms “first effort”, “warm-up”, or “first-hole” angina, have been used to describe the ability of patients to exercise to angina, rest, and then continue exertion with reduced symptoms [2]. In the experimental setting, the salient observation is that at the accumulated external work causing maximum ST-segment depression and chest pain on first exercise, on second exercise there is less ST depression, chest pain and dysrhythmia [3]. During effort, coronary microvascular resistance adapts to match the increase in coronary blood flow to the higher oxygen consumption associated with the increase in heart rate [4-5]. With the onset of effort angina, the adaptation of the microvasculature is exhausted and resistance is thought to be near minimal, beyond the culprit coronary stenosis [6-7]. It is therefore surprising that symptoms and signs of myocardial ischemia can improve on second effort. Thus, the phenomenon of warm-up angina was an enigma that attracted the attention of early pioneers of physiological investigation in the cardiac catheterization laboratory [3,8-13]. These early studies used relatively insensitive techniques such as coronary sinus thermodilution to estimate coronary blood flow and failed to reach a definitive conclusion. More recently, the warm-up angina phenomenon was proposed to be a manifestation of ischemic preconditioning [14], but this theory was refuted by subsequent studies [15-16]. Most recently, it has been suggested that warm up results from reduction in the overall amplitude of the central aortic pressure waveform that has been documented following exercise in healthy volunteers [17-18]. However such changes, while reducing afterload, would be expected to compromise myocardial perfusion in the presence of a flow-limiting coronary stenosis through a reduction in the coronary driving pressure.

The warm-up angina phenomenon is not a mere intellectual curiosity since it is observed in patients taking standard anti-anginal medication [8,19] and reduces ischemic dysrhythmia as well as chest discomfort and ST segment depression [20]. Therefore, if its underlying mechanism could be better understood and mimicked, further therapeutic strategies could be developed.

The purpose of the present study was to investigate these controversies by invasive measurement of aortic pressure and distal coronary pressure and flow velocity during serial exertion in patients with coronary artery disease causing angina.

METHODS

Study population

27 patients were recruited consecutively from routine waiting lists for percutaneous coronary intervention (PCI) at St Thomas’ hospital over the course of 1 year, with symptoms of exertional angina pectoris and a positive exercise treadmill stress test (ETT). The angiographic inclusion criterion was at least one major coronary vessel with a >50% diameter stenosis. Exclusion criteria were unstable symptoms,
previous myocardial infarction/CABG, impaired left ventricular (LV) function, severe co-morbidities, paced rhythm or bundle branch block on ECG or inability to undertake exercise. Patients with left main stem stenoses, severe multi vessel coronary disease, chronic total occlusions or significant visible collateral vessels (Rentrop Class 3+) were not included. Oral nitrate preparations, calcium channel blockers and beta-blockers were stopped at least 48 hours before the procedure.

**Catheter laboratory protocol**

A specially adapted supine cycle ergometer (Ergosana®, Germany) that allows a standardized incremental increase in workload was attached to the catheter lab table. Patients were catheterized via the right radial artery using a standard 6F arterial sheath. Weight adjusted heparin was administered (70u/kg) intra-arterially. Right and left coronary angiograms were then taken using standard diagnostic catheters. Intracoronary nitrates were not used. A standard 6F-guiding catheter was then introduced and positioned in the aortic root. A dual sensor pressure-velocity 0.014” intracoronary wire (Combowire®, Volcano Corp.®, USA)[21] was then connected to the ComboMap® console (Volcano® Corp. USA) and positioned at the tip of the guide. A single sensor 0.014” pressure wire (Brightwire®, Volcano Corp.®, USA) was connected to the ComboMap via an analogue transducer (SmartMap®, Volcano Corp. ®, USA) to provide a high fidelity pressure signal (P_a) that was normalized against aortic pressure measured through the guiding catheter. The pressure wire was then positioned alongside the Combowire at the tip of the guide and the pressure (P_d) on the Combowire was normalized to the pressure wire signal. The guide was then inserted into the coronary ostium and the Combowire advanced distal to the stenosis in the target coronary artery and manipulated until a good Doppler velocity trace was obtained. At this point, the guide was disengaged and the pressure wire was passed into the aortic root and a stable pressure signal obtained. All signals were sampled at 200 Hz and stored on disk for off-line analysis. The data were imported into the custom-made Studymanager program (Academic Medical Center, University of Amsterdam, The Netherlands) and 20 consecutive beats showing good velocity signals were extracted from each minute of exercise and recovery. Averaged signals over each of these time periods were used in further analyses.

**Exercise protocol**

Once wires were in place with good quality and stable signals, baseline measurements were taken before the patient underwent 2 periods of exercise. The exercise protocol was a standardized incremental programme[22] based on the patient’s weight and age, typically starting at 25W and increasing by 20W each minute. Exercise was continued until any of the following occurred, 1) ST depression >3mm, 2) maximal age-related heart rate, 3) severe chest pain, 4) physical exhaustion, 5) occurrence of detrimental effects such as hypotension, severe arrhythmia or dyspnoea. Coronary flow velocity and pressure, ECG, and central arterial pressure were recorded continuously throughout exercise and recovery. After 5 minutes of recovery, or after resting measurements approached baseline, the exercise protocol was repeated. At the end of the study protocol the patient underwent their planned percutaneous revascularization procedure.
Ethics
The study protocol was approved by the local research ethics committee (08/H0802/136) and all participants were provided a detailed information sheet prior to obtaining informed consent.

Data Analysis
All patients had continuous 12-lead ECG monitoring throughout exercise that was analyzed off-line by investigators blinded to patient characteristics and sequence of recordings (i.e. Ex1 or Ex2). The exercise test was considered positive at first appearance of 1mm (0.1 mV) ST-segment depression (STD) 80ms after the J point compared with the resting ECG just prior to exercise. The time of onset of ECG changes signifying exercise test positivity and the corresponding heart rate-central systolic blood pressure product (RPP) were noted.

Central arterial pressure waveforms were obtained from the pressure sensor-tipped guide wire positioned in the aortic root. A typical aortic pressure waveform is shown in Figure 1A. Pulse wave analysis was performed using custom-made programs (Matlab™, The MathWorks Inc®, USA). Augmentation index (AI), a measure of central systolic blood pressure augmentation thought to arise from pressure-wave reflection, was calculated as the difference between the second (P2) and first (P1) peaks expressed as a percentage of the pulse pressure (PP). Timing of the reflected pressure wave (TR) was determined as the time between the foot of the pressure wave (TF) and the inflection point (Pi). The area under the aortic systolic, or tension time index (TTI), and diastolic, or diastolic time index (DTI), portions of the pressure trace were determined using the dichrotic notch (see Figure 1A). The TTI relates to myocardial oxygen demand and DTI to coronary perfusion.[23] The rate pressure product (RPP) was determined from central systolic blood pressure multiplied by heart rate. Left ventricular ejection time (LVET) was measured from the upstroke of the arterial tracing until the trough of the dicrotic notch. At higher heart rates RPP correlates more closely with MV0₂ than does TTI.[24] However, in order to capture changes in the shape of the systolic central aortic pressure trace during exercise we elected to measure both RPP and TTI.

Mean coronary blood flow velocity (U) was determined from the Doppler signal distal to the coronary stenosis. The pressure drop across the coronary stenosis (ΔP) was determined from the mean aortic and distal coronary pressures (Pₐ-Pᵩ). From these data, an index of microvascular resistance (MR) was calculated as Pᵩ/U and an index of coronary stenosis resistance (SR) was calculated as ΔP/U.[21] Wave intensity represents the rate of energy per unit area transported by travelling waves in arteries and is derived from phasic changes in local pressure and flow velocity.[25] In coronary vessels, backward travelling waves are generated by cardiac contraction and relaxation at the downstream end, and forward travelling waves arise from changes in aortic pressure at the inlet.[26-28] Coronary wave intensity hence reflects the interactive effects of cardiac mechanics and coronary conductance on coronary hemodynamics.[27] Wave intensity analysis was performed using custom-made software (Delphi, Embarcadero, San Francisco). The distal pressure and velocity signals were smoothed with a Savitzky-Golay filter to reduce signal noise,[29] and were adjusted to correct for the time delay.
between the digitally archived pressure and velocity signals (55ms). Net coronary wave intensity (dI) was calculated from the time-derivatives of ensemble-averaged coronary pressure and flow velocity as dI= dP/dt x dU/dt.[25,28] Since the aim was to examine coronary perfusion during exercise, and coronary blood flow is predominantly diastolic, we focused our investigation on the flow-accelerating wave at the onset of diastole, the so-called backward expansion wave (BEW); generated by relaxation of the myocardium that sucks blood back into microvascular space.[27-28] The energy carried by the BEW (in J.m⁻².sec⁻² x10⁵) was obtained by the area under the wave and normalized for the sampling interval. The investigators who performed the data analyses were blinded to the sequence of the exercise tests and to the coronary anatomy.

Statistical Analysis
Continuous data are presented as means ± SEM. The study was powered to ensure there were a sufficient number of patients to observe a robust warm up effect on second, compared to first, exertion. This was required as a firm foundation from which to observe associated hemodynamic change. The calculation was based on paired t-tests within subjects, using an anticipated difference of 50 seconds between Ex1 compared to Ex2, with a standard deviation of 27, based on previous research[20]. This gave a sample size of 15 subjects with complete data to achieve 99% power with a probability of a Type 1 error of 0.001. We felt it necessary to achieve at least this level of power since it was likely multiple hemodynamic variables contributed to the warm up effect and their variance was possibly greater than that of the ST-segment. Paired Student’s t-tests were used as indicated. Systemic and coronary parameters were compared between the first and second exertions sessions at each of 4 common time points: baseline (tbaseline), 1 minute (t₁min), 50% of time to peak RPP (t₅₀%) and time of peak RPP (tpeak) during first exertion. Repeated measures analysis of variance (ANOVA) with 2 within-subject factors (exercise and time) were used to compare the common time points between exercise exertions and evaluate the main time trends across exercise periods (IBM® SPSS® Statistics, Version 19). If the overall test for the main effect of exercise exertion reached significance in the ANOVA, we evaluated each separate time point with paired t-tests. We did not apply any correction for multiple comparisons, in order to reduce the chance of missing significant associations in this exploratory study (Type II error).[30] The sphericity assumption, which equates to a compound symmetry correlation structure, was used with the repeated measures ANOVA (IBM® SPSS® Statistics, Version 19). Mauchly’s test of sphericity was used to confirm the sphericity assumption. Relationships between variables were investigated with the Pearson correlation coefficient. P-values were two-sided and values of p<0.05 were considered significant.

RESULTS
Out of 27 patients who were consented into the study 16 (15 male, aged 61±8.9 years) successfully completed the full protocol. Reasons for exclusion were: 4 were found to have left main stem or severe 3-vessel disease on initial angiography; 2
Table 1: Baseline Characteristics, Demographics and Procedural Details

<table>
<thead>
<tr>
<th>Demographics (n=16)</th>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>61 ± 9</td>
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<tr>
<td>Male gender</td>
<td>15 (94)</td>
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<tr>
<td>Previous PCI, n (%)</td>
<td>4 (25)</td>
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<tr>
<td>Previous MI, n (%)</td>
<td>0 (0)</td>
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<tr>
<td>LVEF (%)</td>
<td>65 ± 10</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (31)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>8 (50)</td>
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<tr>
<td>Dyslipidemia, n (%)</td>
<td>10 (62)</td>
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<tr>
<td>Family Hx IHD, n (%)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>4 (25)</td>
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<tr>
<td>β-blockers, n (%)</td>
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<tr>
<td>Nitrates, n (%)</td>
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<tr>
<td>Statin, n (%)</td>
<td>14 (88)</td>
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<tr>
<td>ACEI, n (%)</td>
<td>10 (62)</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Clopidrogel, n (%)</td>
<td>15 (93)</td>
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</table>

Procedural details

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<table>
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<tr>
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<tbody>
<tr>
<td>No. of diseased vessels per pt</td>
<td>1.6 ± 0.7</td>
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<tr>
<td>% stenosis of target lesion</td>
<td>74.6 ± 18.6</td>
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<td>Target lesions undergoing PCI, n (%)</td>
<td>12 (70)</td>
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<tr>
<td>Target vessel (LAD/LCx/RCA)</td>
<td>9/1/6</td>
</tr>
<tr>
<td>Duration of procedure, mins</td>
<td>67 ± 12</td>
</tr>
</tbody>
</table>

PCI = percutaneous coronary intervention; MI = myocardial infarction; LVEF = left ventricular ejection fraction; IHD = ischemic heart disease; LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery

Table 2. Performance and ST Segment Change on First (Ex1) and Second (Ex2) Exercise

<table>
<thead>
<tr>
<th></th>
<th>Ex1</th>
<th>Ex2</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exercise, sec</td>
<td>382 ± 27</td>
<td>405 ± 28</td>
<td>0.08</td>
</tr>
<tr>
<td>Max workload, watt</td>
<td>115.6 ± 6.8</td>
<td>120.3 ± 7.1</td>
<td>0.13</td>
</tr>
<tr>
<td>Pts reaching 1 mm STD, n (%)</td>
<td>15(88)</td>
<td>15(88)</td>
<td></td>
</tr>
<tr>
<td>Time to 1 mm STD, sec</td>
<td>260 ± 31</td>
<td>313 ± 35</td>
<td>0.003</td>
</tr>
<tr>
<td>cRPP at 1 mm STD, mmHg·min⁻¹ x10³</td>
<td>160.7±13.74</td>
<td>178.4±16.3</td>
<td>0.025</td>
</tr>
</tbody>
</table>

STD indicates ST-segment depression on electrocardiograph; cRPP: central rate pressure product.*Compared using paired student t test. '1 patient not included as went into right-bundle-branch block during exercise and ECG nor readable.
were found to have chronic total occlusions; in 2 patients radial arterial access was unsuccessful; 1 patient developed RBBB during exercise (precluding ECG analysis); 1 patient was unable to cycle; 1 patient developed myocardial ischemia very early during first exertion and the ECG was slow to return to baseline. Full background demographics and procedural details are shown in Table 1. With the exception for the reasons of exclusion, there was, for the most part, no significant difference between completers and non-completers in baseline characteristics.

Patients exercised for 382±27 seconds during exertion 1 (Ex1) and for 405±28 seconds during exertion 2 (Ex2), p=0.08. The details of exercise performance are summarized in Table 2. The maximum external workload attained was similar for both efforts. 15 out of the 16 patients (93%) reached 1mm ST-segment depression (STD) during both periods of exercise. Time to 1mm STD was 53±14 seconds longer in Ex2 than Ex1 (p=0.003) confirming warm-up. In addition, the rate pressure product (RPP) at 1mm STD was 12% higher for Ex2 than Ex1 (p=0.025) also consistent with a warm-up effect.

Outcomes of hemodynamic variables are summarized in Figure 2. Despite waiting 8±1.3 minutes for return to baseline after Ex1, heart rate (HR) was higher at the start of Ex2 (p<0.0001), while initial central systolic blood pressure (SBP) was not different. The RPP was correspondingly elevated at the onset of Ex2 compared to Ex1 (p<0.01), although it was not different at t_peak. With increasing HR there was a corresponding rise in SBP during both exercise periods, with a fall in left ventricular ejection time (LVET) and augmentation index (AI). At t_peak SBP was lower in Ex2 than in Ex1 (p<0.001), while LVET was reduced throughout Ex2 even after accounting for the increase in HR (p=0.0009). We also observed a 33% reduction in augmentation index (AI) throughout Ex2 compared to Ex1 (p<0.0001) and augmentation pressure was correspondingly reduced (p<0.0001), also see Figure 1B. Moreover, the degree of warm-up in Ex2 was associated with the change in AI, such that a larger reduction in AI during Ex2 corresponded with a greater increment in RPP at 1mm STD (Pearson r=0.63 95%CI 0.15-0.87, p=0.016). T_R, representing the time for the reflected wave to return to the heart, fell with exercise and remained shorter throughout Ex2 compared to Ex1 (p<0.0001). Despite the increase in systolic blood pressure during each exertion, tension time index (TTI) did not change due to the decrement in pressure augmentation and the changes in LVET. However, TTI was consistently lower during Ex2 (p<0.0001). In contrast, diastolic time index (DTI) fell during both periods with increasing exercise intensity. At the onset of Ex2, the DTI was markedly lower than at the start of Ex1 (p<0.0001), although this can probably be accounted for by the differences in HR. An example of the intra coronary pressure and flow recordings taken at baseline and peak exercise are shown in Figure 3. We observed a progressive fall in microvascular resistance (MR) during Ex1 (p<0.001) with a concomitant 27% increase in coronary flow velocity (p=0.008). See Figure 4. Despite the resulting trend towards a higher pressure drop across the stenosis (ΔP) during exertions, P_d actually increased, which can be explained by the overall increase in mean aortic pressure (p<0.001). In Ex2 the main finding was that MR was consistently lower (p<0.001) resulting in a 16% increase in average coronary flow velocity (p<0.05) compared to Ex1. The increased flow velocity in Ex2 resulted in a corresponding
increase in ΔP (p=0.0001) and fall in $P_d$ (p<0.005) compared to Ex1. Stenosis resistance (SR) was not different between the two exercise periods suggesting no change in functional stenosis severity.

Eleven out of the 16 datasets were suitable for WIA. Exclusions were due to irregular velocity waveforms caused by motion artifacts during exercise, but there were no differences in characteristics compared to the overall patient group. The net energy of the microcirculatory-originating backward travelling expansion, or suction, wave (BEW) increased during each exercise period and was overall 21% higher during Ex2 than Ex1 (p<0.05). See Figure 4. Although an inverse relation was found between the mean values for BEW and MR over both exercise periods (Pearson r=-0.89, 95% CI -0.98 to -0.53, p=0.0025) the average decrease in microvascular resistance (MR) on second exercise was only weakly associated (r=0.2353) with the mean increase in the backward expansion wave (BEW).

**Figure 1:** Panel A shows a typical pressure waveform at rest recorded from the ascending aorta in a healthy middle-aged man. Two systolic peaks are labelled P1 and P2. The area under the curve (AUC) during systole is the tension time index (TTI), and AUC during diastole is diastolic time index (DTI). TR is defined as the time between the foot of the wave (TF) and the inflection point (Pi). Panel B shows an example of an aortic pressure trace from one of the subjects taken at the peak equivalent time point showing the striking change in wave morphology between Ex1 and Ex2, with a reduction in the overall amplitude of the wave and specifically a marked reduction in pressure augmentation.
Figure 2: Systemic parameters derived from aortic pressure at different time points for Ex1 and Ex2. Heart rate (HR) and central systolic blood pressure (SBP) increase during each exercise period. At the time of peak exertion during Ex1, SBP is lower in Ex2. Overall there is no change in rate pressure product (RPP) between Ex1 and Ex2. A reduction in augmentation index (AI) and left ventricular ejection time (LVET) during Ex2 results in a reduction in tension time index (TTI), which is lower throughout Ex2. For the same reason there is also a fall in diastolic time index (DTI) at the beginning of Ex2; $T_r$ is the time for the reflected aortic wave to return and is consistently faster in Ex2 suggesting increased wave speed. *p<0.05, †P<0.001, ‡p<0.0001.
**Figure 3:** The alterations in pressure and flow velocity occurring during serial exercise. The left hand panels were recorded at baseline immediately prior to first (Ex1, upper traces) and second (Ex2, lower traces) exertion. The right hand panels were recorded at peak equivalent workload during Ex1 and Ex2. $P_a =$ proximal, or aortic pressure; $P_d =$ distal coronary pressure; $U =$ coronary flow velocity recorded from the distal coronary artery. The mean flow velocity is higher during Ex2 (27 vs. 22 cm/s, $p=0.03$) causing a greater mean pressure gradient across the coronary stenosis, $\Delta P$ ($P_a - P_d$) (18 vs. 11, $p=0.02$ mmHg) with a resultant reduction in microvascular resistance (3.6 vs. 4.6 mmHg.cm$^{-1}$.sec$^{-1}$, $p=0.01$) that occurs on second effort.
In our study population of patients with severe coronary disease the warm-up angina phenomenon was confirmed on second effort (Ex2). Careful analysis of systemic and coronary hemodynamics during first and second exercise reveals a

**Figure 4:** Coronary parameters at different time points for Ex1 and Ex2. In response to the increased myocardial oxygen demand during exercise, coronary flow velocity (U) increases due to a fall in microvascular resistance (MR). Despite the resulting larger pressure gradient (ΔP) across the stenosis, distal perfusion pressure (P_d) is slightly increased; most likely due to the increasing mean aortic pressure. At the end of Ex1, MR continues to fall, persisting through recovery and remaining low throughout Ex2, with a consequential increase in coronary flow velocity and ΔP in Ex2. As a result, P_d is slightly lower in Ex2. With wave intensity analysis (WIA) the energy of the net backward expansion wave (BEW) is greater on Ex2, suggesting increased microvascular dilatation and enhanced LV relaxation. *p<0.05, †P<0.001, ‡p<0.0001

**DISCUSSION**

In our study population of patients with severe coronary disease the warm-up angina phenomenon was confirmed on second effort (Ex2). Careful analysis of systemic and coronary hemodynamics during first and second exercise reveals a
number of highly significant and interdependent alterations that likely contribute to this effect. Most striking amongst these are 1) a reduction in central aortic pressure augmentation, hence reducing left ventricular work; 2) a reduction in coronary microvascular resistance leading to a higher coronary blood flow velocity; and 3) an increased flow-accelerating backward expansion wave at the onset of diastole, reflecting the important interaction of cardiac-coronary coupling and microvascular conduction with respect to enhancing myocardial perfusion. These combined adaptations synergistically served to alleviate the imbalance between myocardial demand and supply and resulted in the improved performance seen on second exercise.

**Coronary Blood Flow and Oxygen Consumption**
Conceptually and physiologically it is unlikely that increased antegrade blood flow alone is responsible for the beneficial adaptations seen with the warm-up angina phenomenon [10-11]. Warm-up is also unexplained by the recruitment of collateral vessels [20]. Instead, it has been suggested that warm-up is due to attenuation of increased regional myocardial oxygen consumption (MVO2), possibly mediated by adenosine A1 receptor activation, a signaling system known to improve tolerance to ischemia [31]. Bogaty et al., however, were neither able to demonstrate a role for the adaptive down regulation of regional myocardial contractile function during exercise, nor for adenosine-initiated adaptation in patients with warm-up angina [13,15]. Our findings suggest reduced myocardial work during Ex2, with a reduced RPP and TTI at the time point of 1mm STD during Ex1; whilst RPP is more tightly correlated than TTI, both are known determinants of myocardial oxygen consumption [24].

**Arterial Vasodilation and Changes in LV Afterload**
The exercise-induced change to the aortic pressure waveform seen in the present study, i.e. reduced pressure augmentation, is consistent with previous studies [32-34]. It results from reduced peripheral wave reflection due to vasodilation of the systemic muscular arteries [18]. At the equivalent time point at peak exercise in Ex2, the augmentation index was 33% lower than in Ex1. These changes are also consistent with more recent studies in healthy volunteers, where exercise provoked a prolonged reduction in pressure augmentation that persisted for up to 60 minutes into recovery despite stroke volume and carotid-femoral pulse wave velocity returning to baseline [18]. This is a similar time-scale to the persistence of the warm-up effect seen after first exertion in other studies [3,9,20]. In the study by Munir et al., the reduction in pressure augmentation in the aorta was almost identical to that seen following the administration of nitro-vasodilators, suggesting that the reduced tone of muscular arteries together with a reduction in pressure wave reflection from the lower body is an independent mechanism underlying exercise-induced changes in pulse wave morphology [18]. In the present study, improved ventricular-vascular coupling, induced by the favorable and persistent haemodynamic changes following the first episode of exercise, may have contributed to the beneficial adaptation observed during second exercise by reducing afterload and shortening systole. A reduction in ejection duration is associated with enhanced diastolic relaxation [35]. Exercise-induced peripheral
vasodilation has been previously suggested as a potential important mechanism in the warm-up angina phenomenon [17], but this is the first time it has been demonstrated clinically.

**Persistent Decrease in Coronary Microvascular Resistance Index with Exercise**

In the presence of a coronary stenosis the subendocardial myocardium is especially sensitive to impedance of blood flow during systole, and maintenance of uniform transmural myocardial flow distribution is very dependent on changes to microvascular resistance during diastole, especially at increased hearts rates, requiring active coronary vasodilatation [4,6]. It is well established that the subendocardial tissue layer is sensitive to the systolic flow impediment of cardiac contraction, especially in the presence of reduced coronary pressure due to a proximal stenosis [27] and that the resultant hypoperfusion spreads from endocardium to epicardium [4,7]. Subendocardial flow therefore depends critically on diastolic duration [5-6]. At increased hearts rates, as the interval of diastole is reduced, active coronary vasodilatation is required to maintain transmural diastolic perfusion [4-5]. Exercise produces an intense vasodilatory stimulus on the coronary resistance vessels, which substantially alters the relative distribution of blood flow over the coronary vascular bed [36-37]. We observed an increase in coronary flow velocity during Ex1 where MR continued to fall, after an initial slight increase at the start, suggesting progressive vasodilation of the coronary vascular bed with increasing workload. It has been shown that persistent vasomotor tone is present throughout the coronary microcirculation even during ischemia, with substantial vasodilator reserve remaining within the exercising vascular bed of a hypo-perfused region [38]. This is confirmed in the present study, since MR continues to fall after the end of Ex1, through recovery and into the start of Ex2, where the final resistance attained is lower than that which occurred during the myocardial ischemia induced by peak exercise during Ex1 (p=0.0002). The reduction in coronary microvascular resistance we observed during Ex2 indicates a sustained vasodilatory action. Previous studies have suggested that vasodilation may play an important role in warm-up. Joy [8] and Ylitalo [39] used nifedipine and nisoldipine, respectively, in patients demonstrating the warm-up angina phenomenon. In both cases, the addition of these vasodilating agents attenuated the magnitude of warm-up, implying a shared common mechanism. Interestingly, the beta-blocker timolol, which is thought to exert its antianginal effect through reduced myocardial oxygen demand and may cause an increase in α-adrenoceptor mediated coronary vasoconstriction [40], did not attenuate the warm-up response. Bogaty et al. examined the transmural redistribution of coronary blood flow within the myocardium as a mechanism of warm-up using SPECT imaging but was unable to demonstrate any differences, perhaps due to the limited spatial resolution of SPECT [15]. Further studies using high-resolution perfusion imaging to examine changes in subendocardial perfusion may provide insight.
**Coronary-Cardiac Interaction**

In the presence of a severe proximal stenosis (and thereby small residual vasodilator capacity) other factors may also influence transmural distribution of perfusion in response to increased stress. In the setting of myocardial ischemia it is known that changes in myocardial function, including increased compliance and enhanced LV diastolic relaxation contribute to transmural flow redistribution to the subendocardium [41]. Coronary wave intensity analysis reflects the effects of both cardiac contraction and coronary conductance on coronary blood flow dynamics. In the coronary artery, the effects of LV relaxation generate a dominant backward (via the vasculature) expansion wave. This BEW is a flow-accelerating (suction) wave and plays a prominent role in diastolic coronary blood flow [26,28]. A higher magnitude of this wave has been observed after a decrease in microvascular resistance through pharmacological vasodilation [27] and also with enhanced LV relaxation due to a decrease in microvascular compression [26]. Similarly, Davies et al found a 30% reduction in the magnitude of the BEW in patients with LV hypertrophy, a group with known impaired microvascular function and LV relaxation when compared to a group of matched controls [28].

In the present study, although the exercise levels were similar, the magnitude of the BEW was 21% greater on second exertion, which points to an improved myocardial relaxation in early diastole. Since ischemia has been shown to slow diastolic relaxation [42], the higher BEW is consistent with reduced ischemia and consequently, improved coronary blood flow [43]. This important increase in the BEW, together with the beneficial energetics afforded by a reduction in ejection time and LV afterload suggest that enhanced vascular-ventricular coupling, as well as persistent coronary vasodilation and improved cardiac-coronary interaction, play an important role in the improved performance seen on second exertion.

**The Potential Role of Recruitable Coronary Collaterals**

A number of investigators have shown that adaptation to the myocardial ischemia caused by serial intracoronary balloon occlusions is independent of coronary collateral recruitment [20,44-45]. In these studies ischemia is caused by a reduction in myocardial blood supply and hence the model is more akin to ischemic preconditioning rather than warm up angina. Previously, we measured collateral flow index (CFI) during intracoronary balloon inflation accompanying PCI and then compared this value with the magnitude of warm up angina on prior exercise treadmill testing [20]. Although we found no relationship between CFI and warm up, intracoronary balloon occlusion and exercise have recently been shown to differ in their ability to recruit collaterals [46]. In an elegant study of similar design to our present study Togni et al demonstrated an instantaneous increase in CFI in response to dynamic isometric exercise in patients with coronary artery disease [46]. They measured CFI at rest and during the last minute of peak exercise, randomly assigning patients to first measurement either at rest or during exercise. This randomization overcame potential confounding by the ischemic stimulus associated with the one minute of intracoronary balloon inflation needed to measure CFI. There was a significant increase in CFI in response to exercise irrespective of whether CFI was measured first at rest or during exercise. Thus there is no doubt that exercise is a very potent stimulus for collateral recruitment. In the
current study we opted not to measure CFI. Our concern was that coronary artery occlusion would interfere with the patient's ability to exercise, disturb the pattern of myocardial ischemia and prevent us recording intracoronary pressure and flow measurements. Our other concern was that we elected not to measure right atrial/coronary sinus pressure, which is necessary for CFI calculation. Consequently, as suggested previously [47], it is possible that the increase in antegrade coronary flow that we documented on second exertion may also have been augmented by an increase in collateral flow. Thus the mechanisms we identify contribute to a repertoire of adaptations that diminish angina on second effort.

**Study Limitations**

This was a small, single center study but is the first to examine simultaneously the important changes in aortic pressure waveform, patterns of coronary blood flow, and coronary microvascular resistance during large-muscle exercise in the investigation of the warm-up angina phenomenon. In previous non-invasive studies examining warm-up, an interval of 10-15 minutes was used between the repetitive bouts of exercise. Due to practical considerations this was not possible in the current study and the time between exertions was shorter. Consequently, the lingering effects of Ex1 prevented a return to true baseline conditions at the start of Ex2.

We did not measure LV or pulmonary arterial pressures in our study and therefore cannot exclude further differences that may have contributed. We do not expect differences in extra-cellular circulating volumes between Ex1 and Ex2, but previous studies have shown LVEDP to be lower on second exercise, although this did not seem to be related to warm-up [34].

No pharmacological vasodilation was given to keep the environment as close to real-life conditions as possible; minimal resistance was therefore not known. Practical considerations necessitated supine exercise. Such a posture is commonly adopted in diagnostic tests for underlying coronary artery disease and does not appear to impact significantly on sensitivity or specificity [48]. However, supine vs. erect posture is known to influence exercise hemodynamics [49-50]. Nonetheless, we think it unlikely that such considerations influenced our findings since the central hemodynamic changes we observed are similar to those described previously on erect exercise [18] and our main conclusions are based on differences between exertions rather than absolute change during exertion. It is usual when studying warm up angina to perform a delayed third exercise test to document that the warm up effect has waned. This is done to exclude a training component to the improvement on second effort. The nature of our study did not allow a third exercise test and therefore the contribution of training to our findings is unknown.

5 patients were not suitable for WI analysis, which utilizes the first derivative of pressure and velocity waveforms and is therefore particularly affected by the quality of the acquired signals. The average systemic and coronary hemodynamic parameters were comparable between the selected group and the entire study group, and hence our findings from this group likely apply to the whole study population.
CONCLUSIONS

In patients with coronary artery disease who demonstrate the warm-up angina phenomenon, exercise induces vasodilatory changes in the systemic and coronary circulations that reduce central aortic pressure and myocardial microvascular resistance. These combine to improve vascular-ventricular coupling and enhance myocardial perfusion, thereby potentially contributing to the warm-up effect seen on repeat exercise.
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