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

Timothy P.E. Lockie, MBChB, PhD; M. Cristina Rolandi, MSc; Antoine Guilcher, MSc; Divaka Perera, MD; Kalpa De Silva, MBBS; Rupert Williams, MBBS; Kaleb N. Astress, BM, BCh; Kiran Patel, BSc; Sven Plein, MD, PhD; Phil Chowienczyk, MD, PhD; Maria Siebes, PhD; Simon R. Redwood, MD; Michael S. Marber, MBBS, PhD

Background—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 in vivo. In this study we measured central and coronary hemodynamics during serial exercise.

Methods and Results—Sixteen patients (15 male, 61±4.3 years) 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 while 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, a major determinant of left ventricular 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-traveling expansion, or suction, wave on second exercise (P<0.05), indicating improved microvascular conductance and enhanced left ventricular relaxation.

Conclusions—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. (Circulation. 2012;126:2565-2574.)

Key Words: angina, stable ■ exercise ■ physiology ■ pressure

The variable relation between exercise and angina has been recognized for >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.3,4–13 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...
measured through the guiding catheter. The pressure wire was then passed into the aortic root and a stable pressure signal was 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 program based on the patient’s weight and age, typically starting at 25 W and increasing by 20 W each minute. Exercise was continued until any of the following occurred: (1) ST depression > 3 mm, (2) maximal age-related heart rate, (3) severe chest pain, (4) physical exhaustion, or (5) occurrence of detrimental effects such as hypotension, severe arrhythmia, or dyspnea. 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 the planned percutaneous revascularization procedure.

Ethics

The study protocol was approved by the local research ethics committee (08/H0802/136), and all participants were provided with a detailed information sheet before obtaining informed consent.

Methods

Study Patients

Twenty-seven patients were recruited consecutively from routine waiting lists for percutaneous coronary intervention at St. Thomas’ hospital over the course of 1 year, with symptoms of exertional angina pectoris and a positive exercise treadmill stress test. The angiographic inclusion criterion was ≥ 1 major coronary vessel with a >50% diameter stenosis. Exclusion criteria were unstable symptoms, previous myocardial infarction, coronary artery bypass surgery impaired left ventricular (LV) function, severe comorbidities, paced rhythm or bundle-branch block on ECG, or inability to undertake exercise. Patients with left main stem stenoses, severe multivessel coronary disease, chronic total occlusions, or significant visible collateral vessels (Rentrop Class 3+) were not included. Oral nitrate preparations, calcium channel blockers, and β-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 laboratory table. Patients were catheterized via the right radial artery using a standard 6F arterial sheath. Weight-adjusted heparin was administered (70 U/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, San Diego, CA) was then connected to the ComboMap console (Volcano Corp) and positioned at the tip of the guide. A single sensor 0.014” pressure wire (Brightwire, Volcano Corp) was connected to the ComboMap via an analog transducer (SmartMap, Volcano Corp) to provide a high-fidelity pressure signal (Pp) 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 (Pp) 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
by guest on April 17, 2017 http://circ.ahajournals.org/ Downloaded from

expansion wave (BEW); generated by relaxation of the myocardium

accelerating wave at the onset of diastole, the so-called backward
coronary perfusion during exercise, and coronary blood flow is

investigators who performed the data analyses were blinded to
area under the wave and normalized for the sampling interval. The

tion in pressure augmentation.

overall amplitude of the wave and specifically a marked reduc-

demonstrating the striking change in wave morphology between

taken at peak equivalent workload during each exercise period,

between the foot of the wave (TF) and the inflection point (Pi).

during systole is the tension time index (TTI), and AUC during

TR is defined as the time

DTI

areas 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).

Example of an aortic pressure trace from 1 of the subjects

Figure 1. A, Typical pressure waveform at rest recorded from
the ascending aorta in a healthy middle-aged man. Two systolic
peaks are labeled 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).

To observe associated hemodynamic change. The calculation was based
on previous research.20 This gave a sample size of 15 subjects with complete data to achieve 90%

power with a probability of a Type I error of 0.001. We felt it

necessary to achieve at least this level of power because it was likely
multiple hemodynamic variables contributed to the warm-up effect,

and their variance was possibly greater than that of the ST-segment.

Statistical Analysis
Continuous data are presented as means±SEM. The study was
equipped to ensure there were a sufficient number of patients to
observe a robust warm-up effect on second, compared with 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 for time to 1 mm STD between Ex1 compared with 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 90%

power with a probability of a Type I error of 0.001. We felt it

necessary to achieve at least this level of power because 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 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 (t1 minute), 50% of time to peak RPP (ttyp) 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, 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 test of

sphericity was used to confirm the sphericity assumption. Relation-

ships between variables were investigated with the Pearson correla-

tion coefficient. Probability values were 2-sided, and values of

P<0.05 were considered significant.

Results
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 as follows: 4 were
found to have left main stem or severe 3-vessel disease on

initial angiography; 2 were found to have chronic total

occlusions; in 2 patients radial arterial access was unsuccess-

ful; 1 patient developed right bundle branch block 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 de-
tails are shown in Table 1. With the exception of the reasons
of exclusion, there was, for the most part, no significant
difference between completers and noncompleters 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 summa-
ized in Table 2. The maximum external workload attained
was similar for both efforts. Fifteen of the 16 patients (93%)
reached 1 mm STD during both periods of exercise. Time to

1 mm STD was 53±14 seconds longer in Ex2 than Ex1
(P=0.003), confirming warm-up. In addition, the RPP at

1 mm 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 was higher at the start of Ex2
(P<0.0001), whereas initial central systolic blood pressure

backward traveling waves are generated by cardiac contraction and
relaxation at the downstream end, and forward traveling 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 (Del-

phi, Embarcadero, San Francisco, CA). The distal pressure and

velocity signals were smoothed with a Savitzky-Golay filter to

reduce signal noise29 and were adjusted to correct for the time delay

between the digitally archived pressure and velocity signals (55 ms).

Net coronary wave intensity (di) was calculated from the time-

derivatives of ensemble-averaged coronary pressure and flow velocity

as di=dP/dt×dU/dt.25,28 Because 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·×103) 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.
was not different. The RPP was correspondingly elevated at the onset of Ex2 compared with Ex1 ($P<0.01$), although it was not different at $t_{peak}$. With increasing heart rate there was a corresponding rise in systolic blood pressure during both exercise periods, with a fall in LVET and AI. At $t_{peak}$ systolic blood pressure was lower in Ex2 than in Ex1 ($P<0.001$), whereas LVET was reduced throughout Ex2 even after accounting for the increase in heart rate ($P=0.0009$). We also observed a 33% reduction in AI throughout Ex2 compared with 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 1 mm STD (Pearson $r=0.63$; 95% confidence interval, 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 with Ex1 ($P<0.0001$). Despite the increase in systolic blood pressure during each exertion, TTI did not change as a result of the decrement in pressure augmentation and the changes in LVET. However, TTI was consistently lower during Ex2 ($P<0.0001$). In contrast, 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 heart rate.

An example of the intracoronary pressure and flow recordings taken at baseline and peak exercise are shown in Figure 3. We observed a progressive fall in MR during Ex1 ($P<0.0001$) with a concomitant 27% increase in coronary flow velocity ($P=0.008$; see Figure 4). Despite the resulting trend toward a higher pressure drop across the stenosis (AP) 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 with Ex1. The increased flow velocity in Ex2 resulted in a corresponding increase in $\Delta P$ ($P=0.0001$) and fall in $P_{d}$ ($P<0.005$) compared with Ex1. Stenosis resistance was not different between the 2 exercise periods, suggesting no change in functional stenosis severity.

Eleven of the 16 datasets were suitable for wave intensity analysis. Exclusions were a result of irregular velocity waveforms caused by motion artifacts during exercise, but there were no differences in characteristics compared with the overall patient group. The net energy of the microcirculatory-originating backward traveling 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% confidence interval, $-0.98$ to $-0.53$; $P=0.0025$) the average decrease in MR on second exercise was only weakly associated ($r=0.2353$) with the mean increase in the BEW.

### 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 among these are the following: (1) a reduction in central aortic pressure augmentation, hence reducing LV 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 dias-
tolerance, 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. Warm-up is also unexplained by the recruitment of collateral vessels. Instead, it has been suggested that warm-up is a result of attenuation of increased regional myocardial oxygen consumption (MVO₂), possibly mediated by adenosine A₁ receptor activation, a signaling system known to improve tolerance to ischemia. Bogaty et al, however, were neither able to demonstrate a role for the adaptive downregulation of regional myocardial contractile function during exercise, nor for adenosine-initiated adaptation in patients with warm-up angina. Our findings suggest reduced myocardial work during Ex2, with a reduced RPP and TTI at the time point of 1 mm STD during Ex1; although RPP is more tightly correlated than TTI, both are known determinants of myocardial oxygen consumption.

Arterial Vasodilation and Changes in LV Afterload
The exercise-induced change to the aortic pressure waveform seen in the present study (ie, reduced pressure augmentation) is consistent with previous studies. It results from reduced peripheral wave reflection attributable to vasodilation.
of the systemic muscular arteries. 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. This is a similar time-scale to the persistence of the warm-up effect seen after first exertion in other studies. In the study by Munir et al, the reduction in pressure augmentation in the aorta was almost identical to that seen after 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. In the present study, improved ventricular–vascular coupling, induced by the favorable and persistent hemodynamic changes after 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. Exercise-induced peripheral vasodilation has been previously suggested as a potential important mechanism in the warm-up angina phenomenon, 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 vasodilation. It is well established that the subendocardial tissue layer is sensitive to the systolic flow impendence of cardiac contraction, especially in the presence of reduced coronary pressure resulting from a proximal stenosis, and that the resultant hypoperfusion spreads from endocardium to epicardium. Subendocardial flow therefore depends critically on diastolic duration. At increased hearts rates, as the interval of diastole is reduced, active coronary vasodilatation is required to maintain transmural diastolic perfusion. Exercise produces an intense vasodilatory stimulus on the coronary resistance vessels, which substantially alters the relative

![Figure 3. The alterations in pressure and flow velocity occurring during serial exercise. The left panels were recorded at baseline immediately before first (Ex1, upper traces) and second (Ex2, lower traces) exertion. The right panels were recorded at peak equivalent workload during Ex1 and Ex2. Pa indicates proximal, or aortic pressure; Pd, distal coronary pressure; and 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, ΔP (Pa-Pd; 18 vs 11, P=0.02 mm Hg), with a resultant reduction in microvascular resistance (3.6 vs 4.6 mm Hg cm⁻¹ sec⁻¹; P=0.01) that occurs on second effort.](http://circ.ahajournals.org/DownloadedFrom/2570_Circulation_November_27_2012)
distribution of blood flow over the coronary vascular bed.\textsuperscript{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.\textsuperscript{38} This is confirmed in the present study, because MR continues to fall after the end of Ex1, through recovery and remaining low throughout Ex2, with a consequential increase in coronary flow velocity and $\Delta P$ 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. SR indicates stenosis resistance. $^*P<0.05$; $^†P<0.001$; $^‡P<0.0001$

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.\textsuperscript{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.\textsuperscript{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 resulting from a decrease in microvascular compression.\(^{26}\) Similarly, Davies et al.\(^{28}\) 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 with a group of matched controls. 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. Because 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, suggests 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 percutaneous coronary intervention and then compared this value with the magnitude of warm-up angina on previous 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.\(^{46}\) demonstrated an instantaneous increase in CFI in response to dynamic isometric exercise in patients with coronary artery disease. 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 1 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 our 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 may contribute to a repertoire of adaptations that diminish angina on second effort.

**Limitations**

This was a small, single-center study, but it 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 to 15 minutes was used between the repetitive bouts of exercise. Because of 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 extracellular circulating volumes between Ex1 and Ex2, but previous studies have shown left ventricular end-diastolic pressure to be lower on second effort, 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 versus erect posture is known to influence exercise hemodynamics.\(^{49,50}\) Nonetheless, we think it unlikely that such considerations influenced our findings because 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.

Five patients were not suitable for WI analysis, which uses 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.

**Acknowledgments**

Professor J.G.P. Tijssen and N. van Geloven (Academic Medical Centre, Amsterdam, The Netherlands) provided statistical support.
Sources of Funding
This study was funded by British Heart Foundation Clinical Training Fellowships to Dr Lockie (FS08/058/25305), Dr Asrress (FS/11/43/28760), and Dr Williams (FS/11/90/29087) and by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy’s and St Thomas’ National Health Service Foundation Trust and King’s College London. This work was also funded in part by a grant from the European Commission to the Academic Medical Center Amsterdam (FP7-ICT-2007-224495:euHeart). Dr Rolandi was supported by an Academic Medical Centre AMC PhD Scholarship.

Disclosures
None.

References
1. Heberden J. A letter to Dr Heberden, concerning the angina pectoris; and an account of the dissection of one; who had been troubled with that disorder. Medical Transactions, Royal College of Physicians in London. 1785;3:1–11.
Patients with angina often find their symptoms are less pronounced on second compared with first exertion. This is known as the warm-up angina phenomenon, and despite being described >200 years ago it remains poorly understood. The symptomatic benefit provided by the first exertion is still discernible with standard antianginal medication and is accompanied by less ST-segment depression and ischemia-induced dysrhythmia. In patients with angina we investigated the changes in central aortic pressure and coronary artery pressure and flow beyond the culprit stenosis during first and second supine effort in the cardiac catheterization laboratory. These recordings show a number of adaptations during second exercise that act in concert to reduce left ventricular afterload and improve coronary artery blood flow. Amongst the most striking alterations occurring during second exercise are a reduction in augmentation of the central aortic systolic pressure and an increase in the intracoronary pressure wave responsible for accelerating blood flow at the onset of diastole. This pressure wave, known as the backward expansion wave, is dependent both on myocardial vascular tone and rate of relaxation. First exercise triggers adaptive changes within the myocardial and systemic circulations that reduce cardiac work and increase myocardial blood flow during subsequent exercise. These features suggest a novel underlying mechanism that may be harnessed for therapeutic benefit.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
Synergistic Adaptations to Exercise in the Systemic and Coronary Circulations That Underlie the Warm-Up Angina Phenomenon

Timothy P.E. Lockie, M. Cristina Rolandi, Antoine Guilcher, Divaka Perera, Kalpa De Silva, Rupert Williams, Kaleab N. Asrress, Kiran Patel, Sven Plein, Phil Chowienczyk, Maria Siebes, Simon R. Redwood and Michael S. Marber

_Circulation_. 2012;126:2565-2574; originally published online November 1, 2012; doi: 10.1161/CIRCULATIONAHA.112.094292

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/126/22/2565

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/