

Impact of Percutaneous Revascularization on Exercise Hemodynamics in Patients With Stable Coronary Disease



Christopher M. Cook, MBBS, BSc,^a Yousif Ahmad, BMBS,^a James P. Howard, MB BChir,^a
Matthew J. Shun-Shin, BM BCh,^a Amarjit Sethi, MBBS, PhD,^a Gerald J. Clesham, MB BChir, PhD,^{b,c}
Kare H. Tang, MBBS,^b Sukhjinder S. Nijjer, MB ChB, PhD,^a Paul A. Kelly, MB ChB, MD,^b John R. Davies, MBBS, PhD,^{b,c}
Iqbal S. Malik, MBBS, PhD,^a Raffi Kaprielian, MBBS, MD,^a Ghada Mikhail, MBBS, MD,^a Ricardo Petraco, MD, PhD,^a
Firas Al-Janabi, MBBS,^{b,c} Grigoris V. Karamasis, MD,^{b,c} Shah Mohdnazri, MD,^{b,c} Reto Gamma, MD,^b
Rasha Al-Lamee, MBBS,^a Thomas R. Keeble, MBBS, MD,^{b,c} Jamil Mayet, MB ChB, MD, MBA,^a Sayan Sen, MBBS, PhD,^a
Darrel P. Francis, MB BChir, MA, MD,^a Justin E. Davies, MD, PhD^a

ABSTRACT

BACKGROUND Recently, the therapeutic benefits of percutaneous coronary intervention (PCI) have been challenged in patients with stable coronary artery disease (SCD).

OBJECTIVES The authors examined the impact of PCI on exercise responses in the coronary circulation, the microcirculation, and systemic hemodynamics in patients with SCD.

METHODS A total of 21 patients (mean age 60.3 ± 8.4 years) with SCD and single-vessel coronary stenosis underwent cardiac catheterization. Pre-PCI, patients exercised on a supine ergometer until rate-limiting angina or exhaustion. Simultaneous trans-stenotic coronary pressure-flow measurements were made throughout exercise. Post-PCI, this process was repeated. Physiological parameters, rate-limiting symptoms, and exercise performance were compared between pre-PCI and post-PCI exercise cycles.

RESULTS PCI reduced ischemia as documented by fractional flow reserve value (pre-PCI 0.59 ± 0.18 to post-PCI 0.91 ± 0.07), instantaneous wave-free ratio value (pre-PCI 0.61 ± 0.27 to post-PCI 0.96 ± 0.05) and coronary flow reserve value (pre-PCI 1.7 ± 0.7 to post-PCI 3.1 ± 1.0 ; $p < 0.001$ for all). PCI increased peak-exercise average peak coronary flow velocity ($p < 0.0001$), coronary perfusion pressure (distal coronary pressure; $p < 0.0001$), systolic blood pressure ($p = 0.01$), accelerating wave energy ($p < 0.001$), and myocardial workload (rate-pressure product; $p < 0.01$). These changes observed immediately following PCI resulted from the abolition of stenosis resistance ($p < 0.0001$). PCI was also associated with an immediate improvement in exercise time ($+67$ s; 95% confidence interval: 31 to 102 s; $p < 0.0001$) and a reduction in rate-limiting angina symptoms (81% reduction in rate-limiting angina symptoms post-PCI; $p < 0.001$).

CONCLUSIONS In patients with SCD and severe single-vessel stenosis, objective physiological responses to exercise immediately normalize following PCI. This is seen in the coronary circulation, the microcirculation, and systemic hemodynamics. (J Am Coll Cardiol 2018;72:970–83) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Listen to this manuscript's
audio summary by
JACC Editor-in-Chief
Dr. Valentin Fuster.



From the ^aImperial College London, London, United Kingdom; ^bEssex Cardiothoracic Centre, Basildon, United Kingdom; and the ^cAnglia Ruskin School of Medicine, Chelmsford, Essex, United Kingdom. This study was funded in part by the National Institute for Health Research (NIHR) and Imperial College Healthcare NHS Trust Biomedical Research Centre. Drs. Cook (MR/M018369/1), Nijjer (G1100443), and Sen (G1000357) are Medical Research Council fellows. Dr. Howard is a Wellcome Trust fellow (212183/Z/18/Z). Drs. Petraco (FS/11/46/28861), Shun-Shin (FS/14/27/30752), J.E. Davies (FS/05/006), and Francis (FS 04/079) are British Heart Foundation fellows. Drs. Cook, Nijjer, Petraco, and Al-Lamee have received speaker's honoraria from Philips Volcano. Dr. Sethi has been a consultant for Philips Volcano. Dr. Mikhail is course director of the annual Imperial Valve & Cardiovascular Course (IVCC).

In patients with stable coronary artery disease (SCD), the primary treatment goal of percutaneous coronary intervention (PCI) is the relief of angina and improvement in functional capacity. However, the first double-blind, placebo-controlled trial of PCI for stable angina, the ORBITA trial (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) (1), found a far smaller effect on exercise tolerance and symptoms than found in unblinded research (2-4) and in everyday clinical practice. This finding has refocused attention on the need to comprehensively define the therapeutic mechanisms of PCI in SCD.

SEE PAGE 984

Cardiac catheter laboratory protocols have recently been described that enable invasive measurements of coronary and systemic hemodynamics to be performed during supine exercise. Application of these protocols have yielded important mechanistic insight into a variety of anginal conditions. These include the physiological mechanisms underlying the warm-up angina phenomenon (5), the mechanisms of angina in severe aortic stenosis (6), and the alleviation of angina on exertion by sublingual nitroglycerin (7).

In this study, we exercised patients on the coronary catheter laboratory table during cardiac catheterization, immediately before and after PCI. Our hypothesis was that in patients with stable angina and hemodynamically significant single-vessel disease, PCI would immediately improve objectively documented exercise responses in the coronary circulation, the microcirculation, and systemic hemodynamics.

METHODS

STUDY POPULATION. Patients with exertional angina and single-vessel coronary artery disease were recruited from elective PCI waiting lists at both the Hammersmith Hospital and the Essex Cardiothoracic Centre. Inclusion criteria were left ventricular ejection fraction >50% and hemodynamic significance of the target vessel (defined as either fractional flow reserve [FFR] ≤ 0.80 or instantaneous wave-free ratio [iFR] ≤ 0.89). All patients were on maximally tolerated antianginal medical therapy. Exclusion criteria were hemodynamically significant multivessel

disease, left main stem or ostial stenosis, moderate/severe valvular disease, chronotropic incompetence with pacemaker, severe airways disease, or physical inability to exercise. Patients continued all usual medications and were loaded with dual antiplatelet agents as per routine practice of the recruiting center. All subjects gave written informed consent in accordance with the protocol approved by the regional ethics committee (16/LO/1928).

CATHETERIZATION PROTOCOL. The patient was positioned on the catheterization laboratory table and secured to a pre-mounted supine cycle ergometer (Lode Angio, Lode, Groningen, the Netherlands). The ergometer was connected to a laptop computer with software (Lode Export Manager 10, V 10.5.1, Lode) to initiate the exercise protocol and acquire performance data. The target vessel was intubated with a standard 6-F guide catheter from the right radial artery. Intra-arterial unfractionated heparin (70 to 100 U/kg) and intracoronary nitroglycerin (300 μ g) were given before coronary angiography and physiological measurements.

The optimal working view was determined, and a standard coronary guidewire was advanced distally to secure the target vessel. A dual pressure and velocity sensor 0.014-inch intracoronary wire (Combwire XT, Volcano Corporation, San Diego, California) was then advanced to the tip of the guiding catheter, and the pressure signals normalized. The Combwire tip-mounted sensor was advanced distal to the stenosis by a minimum of 15 mm, and its position recorded cineographically. Therefore, 2 wires were positioned in the target vessel for all study measurements. An optimal Doppler velocity trace was obtained by rotational manipulation of the Combwire. Continuous pressure-flow measurements were performed under resting conditions, during a 2-min intravenous infusion of adenosine and during an incremental exercise protocol. The order of adenosine and exercise was randomly assigned. A return to baseline hemodynamic conditions was mandated between each stage of the experimental protocol.

ABBREVIATIONS AND ACRONYMS

BEW	= backward expansion wave
CCS	= Canadian Cardiovascular Score
CFR	= coronary flow reserve
DMR	= diastolic microvascular resistance
DTF	= diastolic time fraction
DTI	= diastolic time index
FCW	= forward compression wave
FFR	= fractional flow reserve
iFR	= instantaneous wave-free ratio
LAD	= left anterior descending coronary artery
PCI	= percutaneous coronary intervention
PP	= pulse pressure
RPP	= rate-pressure product
SCD	= stable coronary disease
TTI	= tension-time index
WIA	= wave-intensity analysis

which is supported by Edwards Lifesciences, Abbott, Medtronic, Philips, Volcan, Occlutech, Acist, Cordis, CryoLifeEuropa, and LivaNova. Dr. Keeble has received research grants from Philips Volcano. Dr. Mayet hold patents pertaining to iFR technology. Dr. Sen has received speaker honoraria from Philips Volcano, Pfizer, and AstraZeneca. Dr. J.E. Davies holds patents pertaining to iFR technology; and has been a consultant for and received research grants from Philips Volcano. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 26, 2018; revised manuscript received June 7, 2018, accepted June 9, 2018.

TABLE 1 Reasons for Noncompletion of the Full Study Protocol

Could not validly exercise	
Required femoral access	2
Sedation required	2
Acute target vessel occlusion requiring immediate PCI	1
Became ineligible after angiogram and/or physiological assessment	
Operator decision to defer PCI based on FFR/iFR	7
Operator decision to refer for LIMA to LAD	2
Found to have developed CTO	1
Ventricular fibrillation	1
Could not perform post-PCI exercise	
Plan for ostial LAD stenting was changed to cover left main stem (exclusion criterion)	1
After PCI, had persistent low-level chest discomfort preventing symptom-limited exercise	1
Technical difficulties	
Unable to acquire satisfactory quality velocity data	5
Research equipment dysfunction preventing adequate data acquisition	2
Values are n.	
CTO = chronic total occlusion; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LAD = left anterior descending coronary artery; LIMA = left internal mammary artery; PCI = percutaneous coronary intervention.	

Before removal from the patient, the Combwire was returned to the catheter tip to assess for pressure drift. Angioplasty was then performed according to standard clinical practice. Stent optimization was performed at the operator's discretion. Following angioplasty, the Combwire was reintroduced, advanced to the guiding catheter tip, and then renormalized as before. The Combwire was advanced to the same intracoronary position as previous, with cross-reference to the cine-acquired roadmap image for confirmation. All aforementioned stages of the pre-PCI study protocol were then repeated, including the incremental exercise protocol.

EXERCISE PROTOCOL. An incremental exercise protocol starting at 40 W and increasing by 20 W every minute was used for all patients. The guiding catheter was disengaged from the coronary ostium for the duration of exercise to prevent vessel trauma and to permit central aortic pressure waveform recording without damping. Exercise was continued until the development of rate-limiting angina symptoms or physical exhaustion. Systemic serum lactate levels were measured from arterial blood drawn from the guiding catheter immediately before and at peak exercise in order to quantify the rise in serum lactate during exercise.

DATA ANALYSIS. The electrocardiogram, pressure waveforms, and coronary flow velocity signals were directly extracted from the digital archive of the device console (ComboMap, V 1.9, Volcano Corporation)

TABLE 2 Baseline Characteristics

Demographics	
Age, yrs	60.3 ± 8.4
Male	19 (91)
Diabetes	1 (5)
Hypertension	15 (71)
Hyperlipidemia	15 (71)
History of smoking	8 (38)
Family history of ischemic heart disease	4 (19)
Previous myocardial infarction	2 (10)
LVEF <40%	0 (0)
CCS class	
I	1 (5)
II	8 (38)
III	12 (57)
Medications	
Aspirin	21 (100)
Clopidogrel	21 (100)
Beta-blockers	16 (76)
Statin	20 (95)
ACE inhibitors/ARB	16 (76)
Nitrates	6 (29)
CCB	8 (38)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

for offline analysis. Wave-intensity analysis (WIA) was performed according to methodology as previously described (8). Exercise data were exported from the ergometer software package using a dedicated export manager (Lode Export Manager 10, V 10.5.1,

TABLE 3 Procedural Details

Target vessel (LAD/Cx/RCA)	11/6/4
Stenosis location (proximal/mid/distal)	13/6/2
Area stenosis by QCA, %	93.1 ± 5.7
Diameter stenosis by QCA, %	75.7 ± 10.3
Stenosis length, mm	11.0 ± 4.13
FFR	0.59 ± 0.18
iFR	0.61 ± 0.27
CFR	1.7 ± 0.7
HSR	2.3 ± 2.3
Stent length, mm	23 ± 8.3
Stent diameter, mm	3.3 ± 0.4
Stent post-dilatation	86 (18/21)
FFR post-PCI	0.91 ± 0.07*
iFR post-PCI	0.96 ± 0.05*
CFR post-PCI	3.1 ± 1.0*
HSR post-PCI	0.2 ± 0.2*

Values are n, mean ± SD, or % (n/N). *Significant difference pre- versus post-PCI; p < 0.0001.

CFR = coronary flow reserve; Cx = circumflex coronary artery; HSR = hyperemic stenosis resistance; QCA = quantitative coronary angiography; RCA = right coronary artery; other abbreviations as in Table 1.

Lode, Groningen). Functional parameters quantified were exercise time (seconds), maximum workload (Watts), energy expenditure (kilojoules), and peak metabolic equivalent.

PULSE WAVE ANALYSIS OF CENTRAL AORTIC PRESSURE. Central arterial pressure waveforms were obtained from the fluid-filled guiding catheter in the aortic root. A custom-made software package (PyCharm CE, V 2017.2.4) was used to analyze a minimum of 5 consecutive ensemble-averaged cardiac cycles through electrocardiogram gating. Semi-automatic identification of the upstroke and peak of the arterial tracing and the trough of the dichrotic notch permitted calculation of the tension-time index (TTI) (relating to myocardial oxygen demand [9]), diastolic time index (DTI) (relating to coronary perfusion [10]), diastolic time fraction (DTF), and pulse pressure (PP). The rate-pressure product (RPP) is a surrogate marker of myocardial oxygen consumption and myocardial workload (11), and was calculated as the product of central systolic blood pressure and heart rate.

STATISTICAL ANALYSIS. Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were expressed as mean \pm SD (unless otherwise specified). Categorical variables were expressed as numbers and percentages. Continuous variables were compared with paired Student's *t*-tests. Categorical variables were compared with chi-square tests. Repeated measures analysis of variance was used to evaluate trends across the stages of exercise pre- and post-PCI. If significant, differences in separate exercise stages were evaluated with paired *t*-tests. Applicable tests were 2 tailed, and $p < 0.05$ was considered statistically significant. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION. Twenty-one patients (19 male; age 60.3 ± 8.4 years) completed the study protocol. A total of 46 patients were consented to the study but were unable to complete the protocol for the following reasons: could not validly exercise ($n = 5$), became ineligible after coronary angiogram and/or physiological assessment ($n = 11$), could not perform post-PCI exercise ($n = 2$), or technical difficulties prevented data acquisition ($n = 7$). A full breakdown of the reasons for noncompletion of the full study protocol is listed in Table 1.

The baseline characteristics of the study population are summarized in Table 2. The majority of patients were in Canadian Cardiovascular Society

(CCS) class 2 or 3 at enrollment. The mean number of prescribed antianginal medications per patient was 1.4 ± 0.7 .

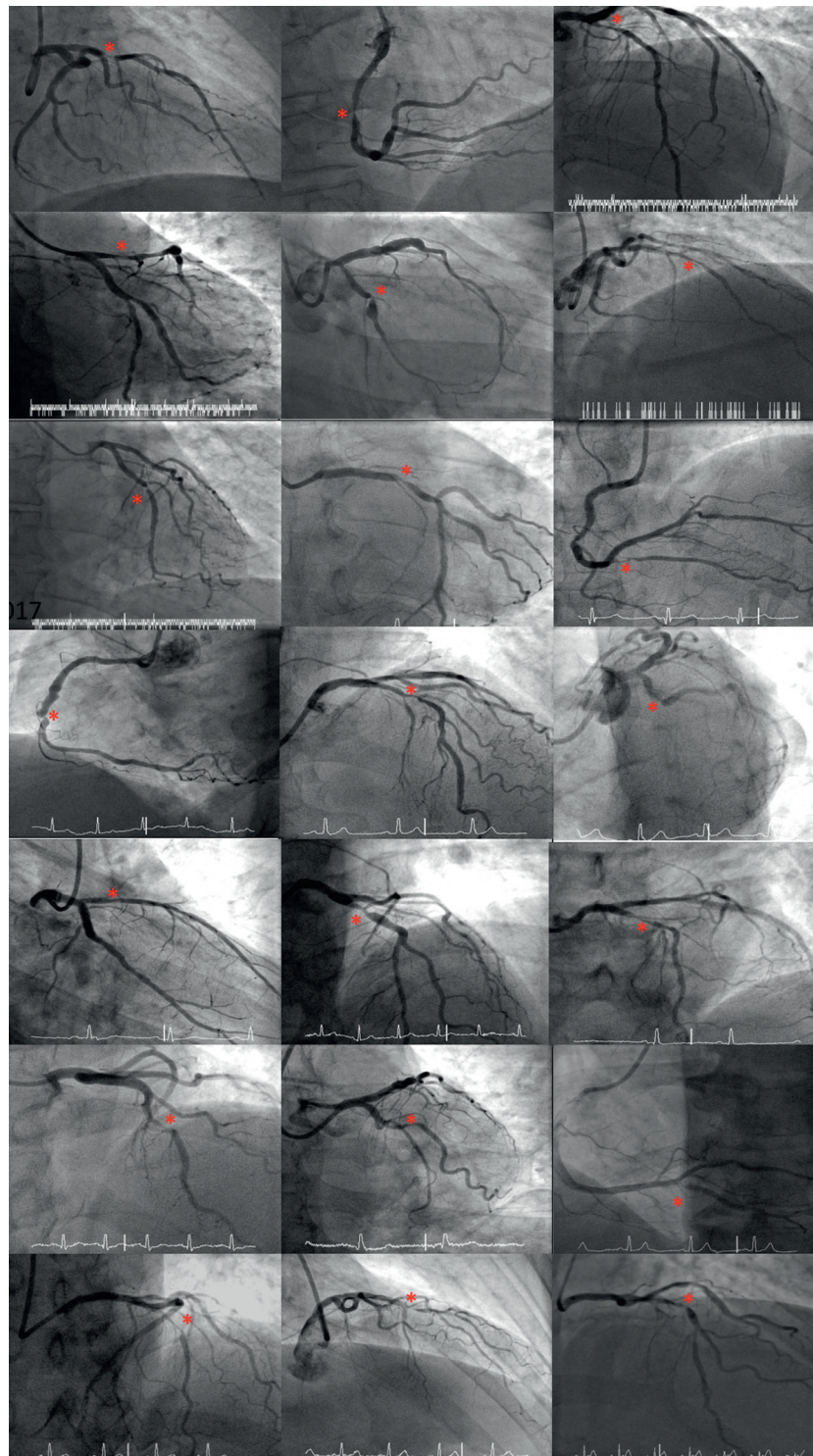
STENOSIS AND PROCEDURAL CHARACTERISTICS.

Stenosis characteristics are shown in Table 3 and in Figure 1. The stenoses were angiographically and physiologically severe. Mean stenosis diameter by quantitative coronary angiography was $75.7 \pm 10.3\%$. FFR averaged 0.59 ± 0.18 , iFR 0.61 ± 0.27 , coronary flow reserve (CFR) 1.7 ± 0.7 , and hyperemic stenosis resistance (HSR) 2.3 ± 2.3 .

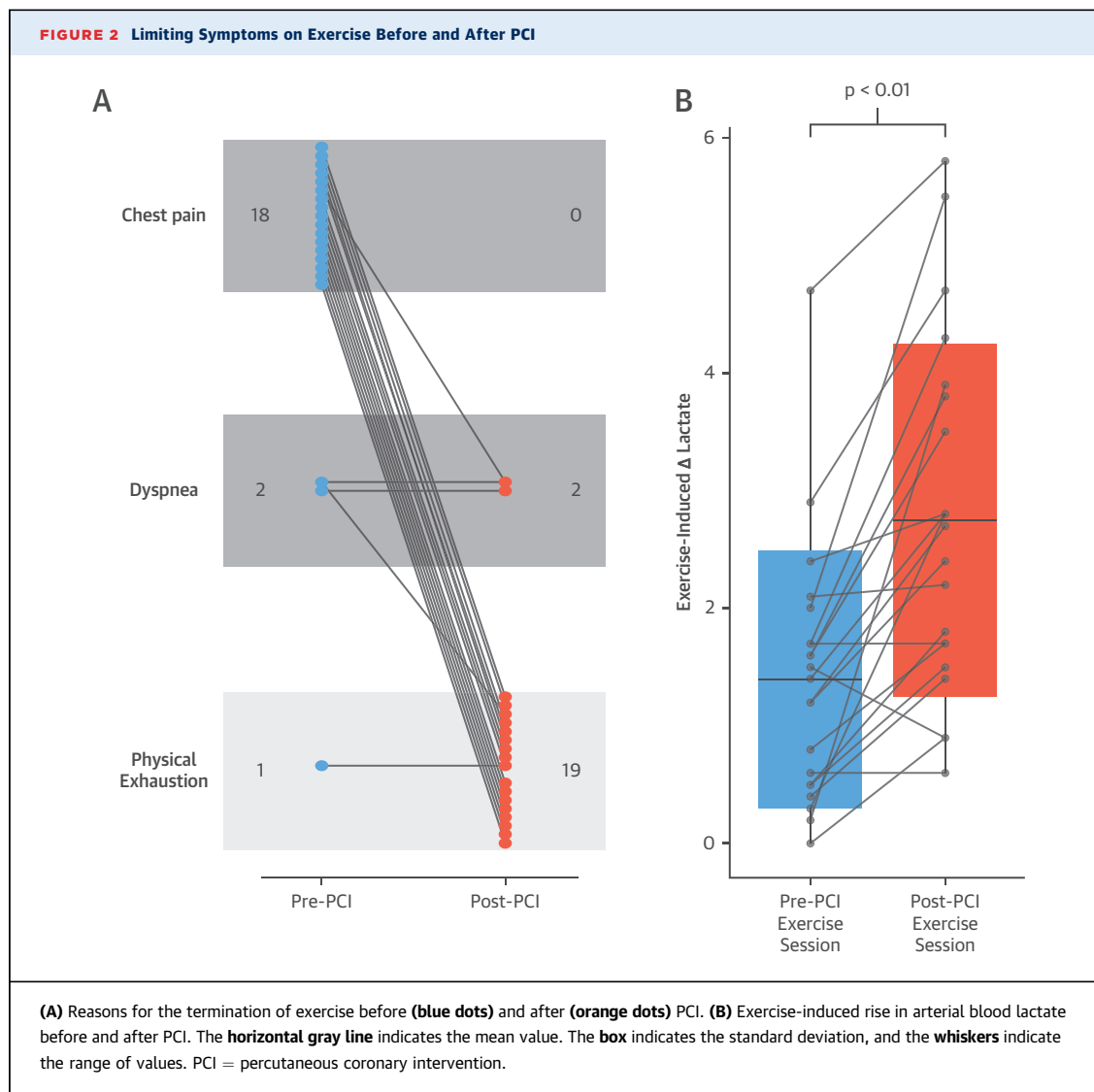
All stenoses were focal and were predominantly proximal (62% [13 of 21]), most frequently in the left anterior descending coronary artery (LAD) (52% [11 of 21]). All PCIs were performed successfully with drug-eluting stents. The mean number of stents implanted per patient was 1.0 ± 0.2 , the mean length of stent was 23 ± 8.3 mm, and the mean diameter of stent was 3.3 ± 0.4 mm. Post-dilatation was performed in 18 of 21 stents (86%). Post-PCI, FFR rose to 0.91 ± 0.07 , iFR to 0.96 ± 0.05 , and CFR to 3.1 ± 1.0 , and hyperemic stenosis resistance fell to 0.2 ± 0.2 ($p < 0.0001$ for all).

SYMPTOM AND EXERCISE RESPONSES. Before PCI, 95% of patients stopped exercising because of chest pain or breathlessness (Figure 2). By contrast, after PCI, only 10% did so, with the remainder stopping because of physical exhaustion without chest pain or breathlessness. Before PCI, baseline serum lactate was 1.0 ± 0.41 mmol/l, and this increased to 2.4 ± 1.1 mmol/l at peak exercise (+240%). After PCI, baseline serum lactate was 1.3 ± 0.51 mmol/l, and this increased to 4.1 ± 1.8 mmol/l at peak exercise (+315%; $p < 0.001$ for the difference in increment of serum lactate during exercise). Exercise time increased by 67 s (95% confidence interval: 31 to 102 s; $p < 0.001$) (Figure 3) after PCI. Full exercise performance data are shown in Table 4.

SYSTEMIC HEMODYNAMIC RESPONSES. Before PCI, blood pressure initially rose progressively with exercise but then fell at peak exercise when symptoms developed (peak exercise 7.7 mm Hg below the preceding time point; $p = 0.01$) (Figure 4). After PCI, blood pressure rose initially again; however, at peak exercise, blood pressure plateaued and did not decline. Corresponding to peak exercise in the pre-PCI state, at the equivalent exercise time point in the post-PCI state, blood pressure was significantly higher (delta 14.0 mm Hg; $p = 0.01$). Because patients could exercise for longer following PCI, an extra time point at an even higher workload was recorded, and again this was significantly higher than peak exercise during the pre-PCI state (delta 12.0 mm Hg; $p = 0.02$). The same pattern was seen for RPP.

FIGURE 1 Coronary Angiograms of the 21 Included Patients

The target lesion is marked with a red asterisk.

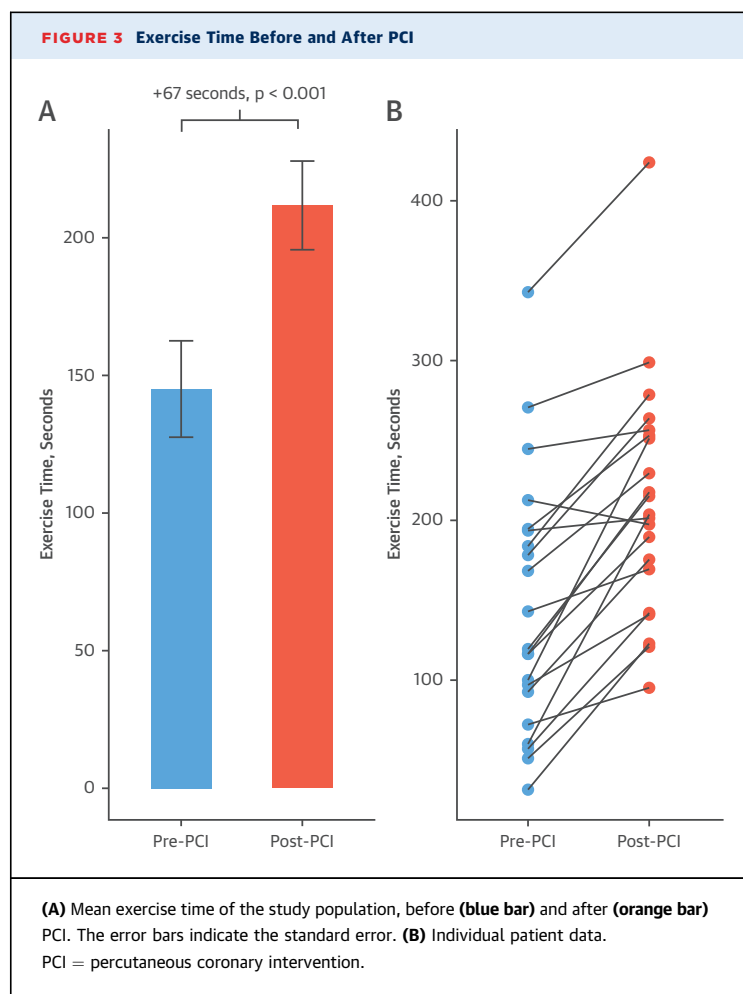


Analysis of central arterial pressure waveforms during exercise are summarized in [Figure 5](#). PP increased with exercise ($p < 0.001$) both before and after PCI. Because both heart rate and systolic blood pressure increased together, TTI did not increase significantly during exercise ($p = 0.51$). In line with the overall increase in heart rate (and thus shortening of diastole), DTI and DTF both decreased significantly with exercise ($p < 0.0001$). Changes in PP, TTI, DTI, and DTF during exercise were similar both before and after PCI ($p > 0.05$ for all). Full systemic hemodynamic responses are shown in [Table 5](#).

CORONARY AND MICROCIRCULATORY HEMODYNAMIC RESPONSES. Coronary circulation and microvascular responses to exercise are summarized in [Figure 6](#). Resting coronary flow velocity was similar both

before and after PCI ($p = 0.19$). Flow significantly increased during both pre- and post-PCI exertions ($p = 0.03$) but displayed markedly different patterns of rise ($p < 0.01$). Before PCI, coronary flow velocity increased minimally with exercise and plateaued early. Conversely, after PCI, coronary flow velocity increased in a near-linear fashion with exercise and was significantly higher for all time-matched stages of exercise ($p < 0.0001$). At peak exercise, coronary flow velocity was 65% higher after PCI than before (18.2 ± 7.7 cm/s vs. 30.1 ± 8.6 cm/s; $p < 0.0001$).

Distal coronary pressure, trans-stenotic pressure gradient, trans-stenotic pressure ratio (P_d/P_a) and stenosis resistance were all markedly improved at all stages of exercise following PCI ($p < 0.0001$ for all) ([Table 5](#)). The reduction in global microvascular resistance during exercise was similar both before



and after PCI ($p = 0.60$) (Online Figure 1). However, diastolic microvascular resistance (DMR), the portion of the cardiac cycle where myocardial compressive forces are at their lowest (12), was significantly lower at rest before PCI ($p = 0.04$) (Figure 6). Furthermore, the pattern of decline in DMR was different ($p = 0.01$) before versus after PCI. Before PCI, DMR reached its minimum value earlier during exercise than in the

TABLE 4 Exercise Performance Data Before and After PCI

	Pre-PCI	Post-PCI	p Value
Exercise time, s	145 ± 80	212 ± 74	<0.001
Distance covered, m	529 ± 484	854 ± 571	<0.01
Max workload, W	83 ± 30	103 ± 30	<0.01
Max intensity, MET	4.3 ± 1.2	5.2 ± 1.2	<0.01
Total energy expenditure, kJ	7.9 ± 7.3	13.1 ± 8.5	<0.01
Rate-pressure product	12,515 ± 3,697	14,903 ± 3,897	<0.01

Values are mean ± SD.
MET = metabolic equivalent; PCI = percutaneous coronary intervention.

post-PCI state. Full coronary and microcirculatory hemodynamic responses are shown in Table 5.

Eighteen of the 21 paired datasets were suitable for WIA. The 2 waves that accelerate flow are the backward expansion wave (BEW) and the forward compression wave (FCW) (8). Exercise WIA data are summarized in Online Figure 2. The absolute values of BEW intensity and FCW intensity at rest and at peak exercise are displayed in Figure 7. At rest, net wave intensity of the flow accelerating waves was similar both pre- and post-PCI ($p = 0.42$). However, at peak-exercise post-PCI, net wave intensity of the flow accelerating waves was significantly higher than at peak exercise pre-PCI ($p = 0.01$).

The contribution to flow acceleration by backward expansion and forward compression waves was different at rest and at peak exercise before versus after PCI. In comparison between the pre- and post-PCI resting states, BEW intensity was significantly lower ($p = 0.04$), and FCW intensity was significantly higher ($p = 0.03$) following PCI. In comparison between the pre- and post-PCI peak-exercise states, BEW intensity was similar ($p = 0.32$), and FCW intensity was significantly higher ($p = 0.02$) following PCI.

DISCUSSION

This study shows that coronary flow and pressure cannot rise to meet the demands of physical exercise when there is a significant coronary stenosis. PCI immediately normalizes the ability of coronary flow and pressure to rise to match this myocardial demand.

Second, PCI improves coronary, microvascular, and systemic hemodynamic responses to exercise. By abolishing stenosis resistance with instantaneous effect, PCI restores the coronary vessel to its primary role as a conduit and the capacity of the microcirculation to progressively vasodilate during exercise.

Third, in patients with stable angina and physiologically significant single-vessel disease unblinded to the fact that they have received PCI, PCI immediately improves exercise capacity and reduces rate-limiting angina symptoms (Central Illustration).

Last, in contrast to the traditional advice that patients should only resume exercise in a delayed and graduated fashion following PCI, this study demonstrates the safety of performing maximal physical exercise immediately after coronary stenting.

PCI AND CHANGES IN THE CORONARY CIRCULATION RESPONSE TO EXERCISE. Because oxygen extraction is near maximal even at rest (13), the principal way myocardial oxygen demand on exercise can be met is

through an increase in coronary blood flow (14). We found that coronary flow increased in very different ways before versus after PCI. Before PCI, coronary flow plateaued early during exercise. This can be explained by both mechanical limitation to flow from the stenosis, manifesting as high stenosis resistance, and premature maximal dilatation of the microcirculatory vascular bed.

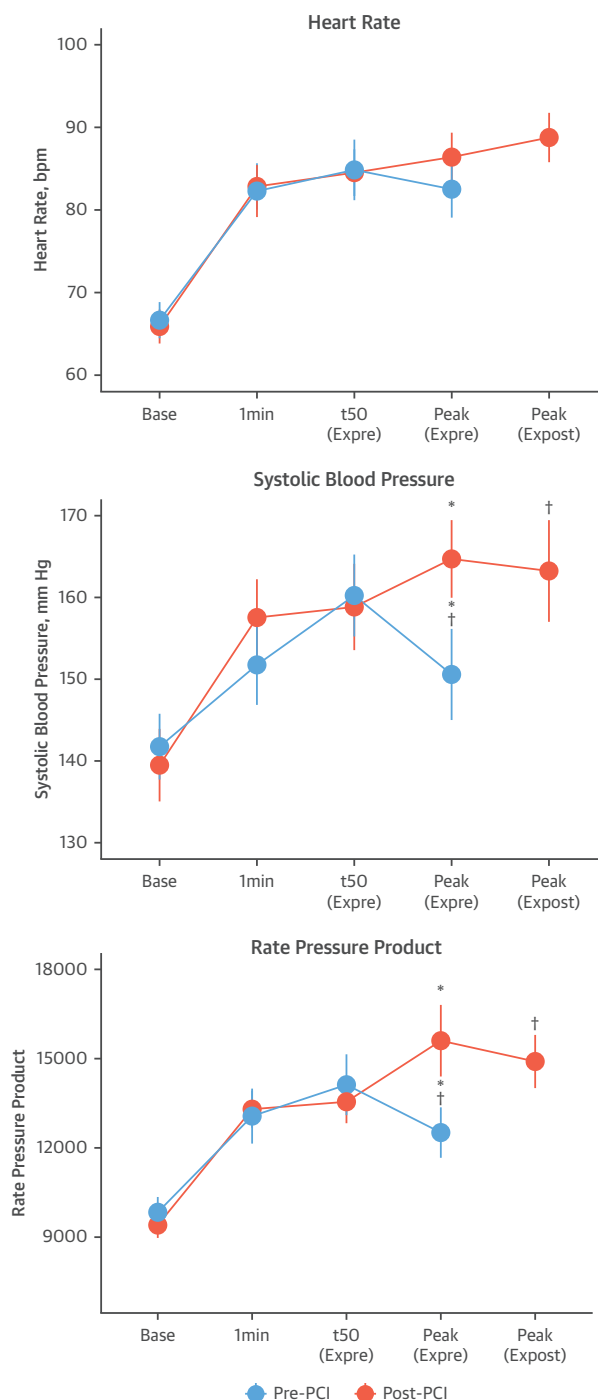
Immediately after PCI, flow increased almost linearly with exercise and was significantly higher at all stages of exertion by comparison with the corresponding pre-PCI measurements. This was due to a large fall in stenosis resistance and a corresponding increase in microcirculatory resistance at rest. These physiological adaptations following PCI restored the coronary vessel to its primary role as a conduit (15) and also restored the capacity of the downstream microcirculatory bed to progressively vasodilate during exercise.

Exercise coronary pressures, too, showed a different pattern after PCI than before. Distal coronary pressure is effectively the pressure perfusing the coronary bed (14). Before PCI, distal coronary pressure was low at rest, rose slightly during early exercise, but actually fell again at peak-exercise, culminating in hypoperfusion of the coronary bed. The fall in distal coronary pressure before PCI may have been the result of the concomitant fall in aortic driving pressure that was also observed. After PCI, distal coronary pressure started higher, rose slightly, and then was maintained. This is consistent with normalization of the coronary perfusion response to exercise.

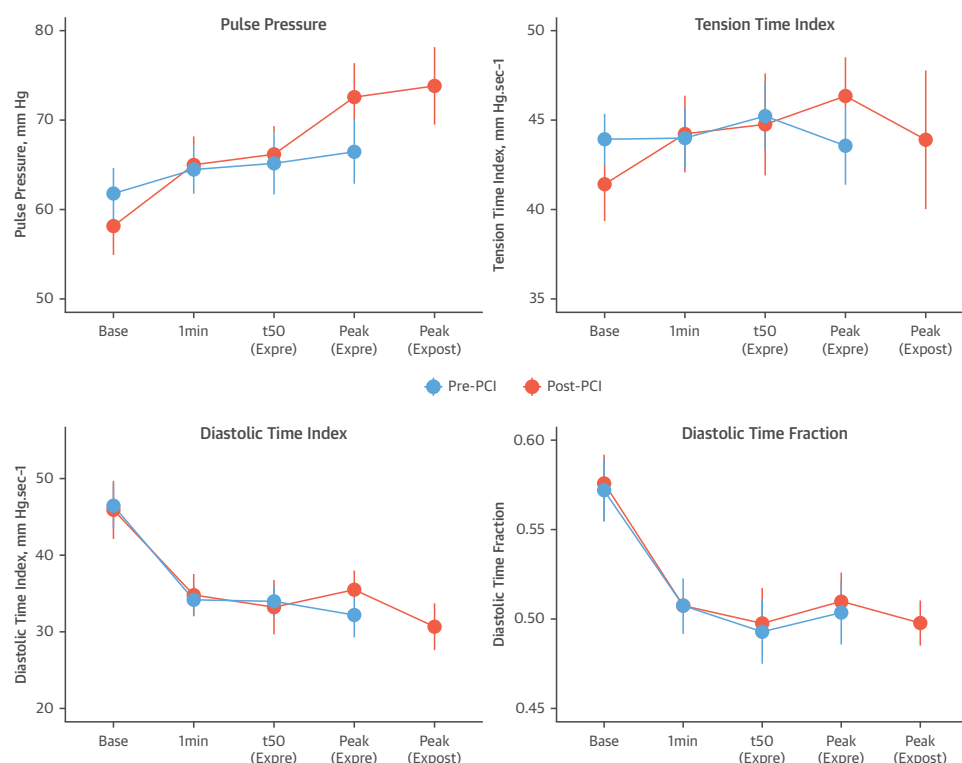
PCI AND CHANGES IN THE MICROCIRCULATORY RESPONSE TO EXERCISE. In health, the large increase in coronary flow necessary during physical exercise is achieved predominantly by a large fall in microvascular resistance (16). When there is a hemodynamically significant coronary stenosis, lowering distal coronary pressure, this process of vasodilatation is enacted even at rest. This homeostatic mechanism, termed coronary autoregulation (17,18), allows perfusion to be adequate at rest despite a large stenosis resistance in the resting state. During exercise, however, because this microcirculatory vasodilatation has already been exhausted to maintain resting coronary flow, there is little remaining capacity to vasodilate to accommodate the necessary increase in flow.

PCI eliminates the stenosis resistance and thereby eliminates the need for microcirculatory vasodilator capacity to be consumed at rest. As shown in Figure 6, the resting diastolic microcirculatory resistance is higher than before PCI. It decreases progressively

FIGURE 4 Systemic Hemodynamic Responses to Exercise



Heart rate, systolic blood pressure, and rate-pressure product responses to exercise at baseline (Base), 1 min of exercise (1 min), 50% of the pre-PCI time (t50Expre), peak-exercise time pre-PCI (PeakExpre), and peak-exercise time post-PCI (PeakExpost), before (blue) and after (orange) PCI. The error bars indicate the standard error. *Significant difference between time-matched exercise stages pre- versus post-PCI; $p < 0.05$. †Significant difference between peak-exercise pre- versus post-PCI; $p < 0.05$. PCI = percutaneous coronary intervention.

FIGURE 5 Aortic Pressure Waveform Responses to Exercise

Pulse pressure, tension time index, diastolic time index, and diastolic time fraction responses to exercise, before (blue) and after (orange) percutaneous coronary intervention.

with exercise, and by peak exercise, it has fallen to the same level as pre-PCI peak exercise. This suggests that the microcirculation is not inherently affected by PCI, but that PCI restores the conduit function of the epicardial artery so that the microcirculatory vasodilatory capacity can be reserved for use during exercise.

Whether the stimulus to increase coronary flow is pharmacological vasodilatation or the increased myocardial demand from physical exercise, if part of the microcirculatory vasodilatory capacity has already been used to maintain resting coronary flow, then less vasodilator capacity remains to further increase flow. This mechanism also explains the low CFR observed in our patients before PCI that was subsequently restored to normal following stenting.

EFFECT OF PCI ON SYSTEMIC HEMODYNAMIC RESPONSES TO EXERCISE. During physical exercise, heart rate, systolic blood pressure, and ventricular

contractility normally increase (14). In our patients before PCI, at peak exercise there was a reversal of this pattern with a fall in blood pressure and heart rate, and therefore in the RPP. This may be a systemic manifestation of an inability of myocardial perfusion to increase adequately in the territory subtended by the stenosed artery. In support of this interpretation, after PCI, at the identical level of exercise, the blood pressure and RPP were significantly higher.

Pulse wave analysis of aortic pressure waveforms during exercise did not reveal any significant differences before versus after PCI. This is in contrast with the findings of previous catheter laboratory exercise studies investigating the warm-up angina phenomenon (5) and the physiological effect of sublingual nitroglycerin in patients with stable angina (7). Within those studies, in the absence of PCI, significant lowering of afterload, the tension time index, and the Buckberg index was observed on repeat

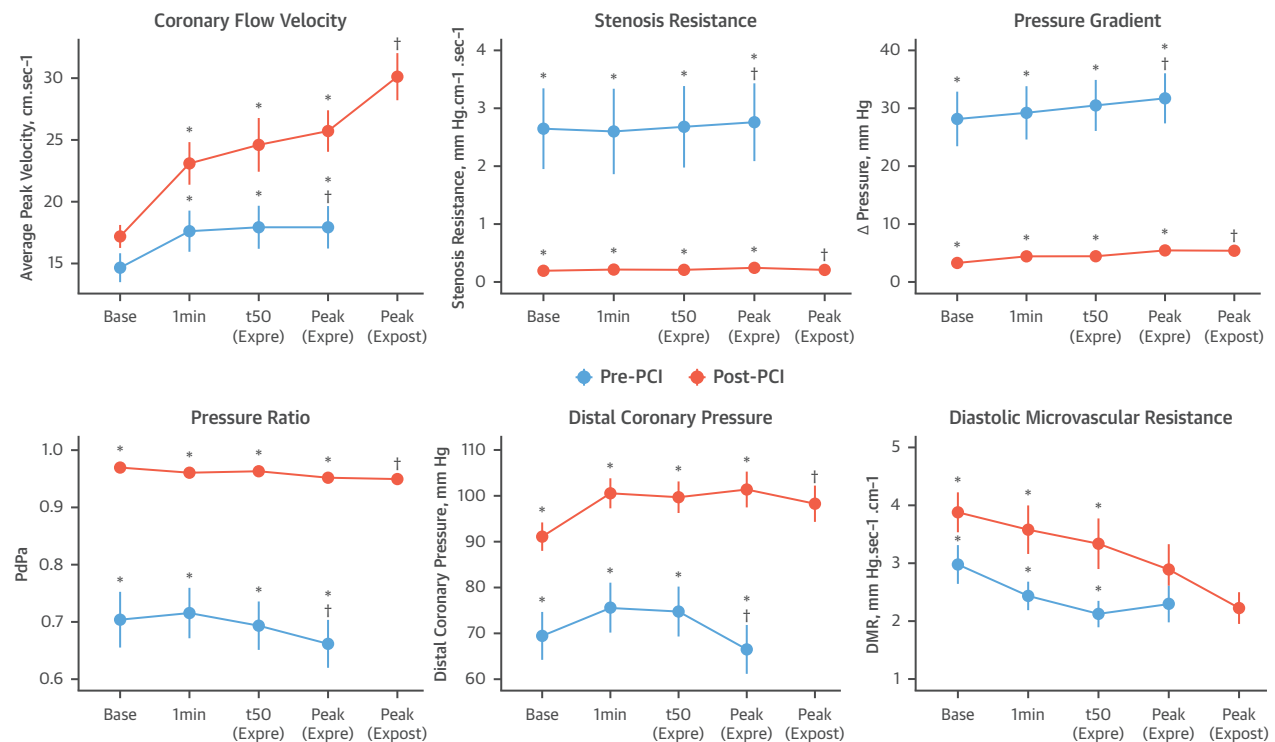
TABLE 5 Systemic, Coronary, and Microcirculatory Hemodynamic Responses to Exercise Before and After PCI

	Pre-PCI				Post-PCI					p Value (ANOVA)
	Baseline	1 Min	t50 (Expre)	Peak (Expre)	Baseline	1 Min	t50 (Expre)	Peak (Expre)	Peak (Expost)	
HR, beats/min	67 ± 13	83 ± 18	85 ± 22	83 ± 20	66 ± 12	83 ± 17	85 ± 16	86 ± 17	88 ± 17	0.19
SBP, mm Hg	142 ± 18	152 ± 21	160 ± 21	151 ± 24	140 ± 19	158 ± 20	159 ± 22	165 ± 20	163 ± 26	0.004
RPP	9,836 ± 2,355	13,069 ± 3,920	14,122 ± 4,458	12,515 ± 3,697	9,405 ± 1,931	13,301 ± 2,710	13,550 ± 3,140	15,603 ± 5,242	14,903 ± 3,897	0.02
PP, mm Hg	62 ± 11	65 ± 10	65 ± 13	66 ± 13	58 ± 12	65 ± 11	66 ± 10	73 ± 12	74 ± 14	0.35
TTI, mm Hg · s ⁻¹	44 ± 6	44 ± 6	45 ± 7	44 ± 8	41 ± 8	44 ± 8	45 ± 10	46 ± 7	44 ± 13	0.68
DTI, mm Hg · s ⁻¹	46 ± 12	34 ± 7	34 ± 8	32 ± 11	46 ± 15	35 ± 10	33 ± 12	36 ± 8	31 ± 10	0.90
DTF	0.57 ± 0.07	0.51 ± 0.06	0.49 ± 0.07	0.50 ± 0.07	0.58 ± 0.06	0.51 ± 0.05	0.50 ± 0.07	0.51 ± 0.05	0.50 ± 0.05	0.86
APV, cm/s	15 ± 5	18 ± 7	18 ± 8	18 ± 8	17 ± 4	23 ± 8	25 ± 10	26 ± 7	30 ± 9	0.002
SR, mm Hg · cm ⁻¹ · s ⁻¹	2.7 ± 3.1	2.60 ± 3.2	2.7 ± 3.1	2.8 ± 2.9	0.19 ± 0.25	0.21 ± 0.24	0.21 ± 0.21	0.24 ± 0.19	0.21 ± 0.18	<0.001
ΔP, mm Hg	28 ± 21	30 ± 20	31 ± 20	32 ± 19	3 ± 4	4 ± 5	5 ± 4	6 ± 5	5 ± 5	<0.001
PdPa	0.70 ± 0.22	0.72 ± 0.19	0.69 ± 0.18	0.66 ± 0.19	0.97 ± 0.04	0.96 ± 0.04	0.96 ± 0.04	0.95 ± 0.04	0.95 ± 0.05	<0.001
Pd, mm Hg	69 ± 23	76 ± 24	75 ± 25	66 ± 24	91 ± 14	101 ± 14	100 ± 16	102 ± 17	98 ± 18	<0.001
DMR, mm Hg · cm ⁻¹ · s ⁻¹	3.0 ± 1.4	2.4 ± 1.1	2.1 ± 1.0	2.3 ± 1.4	3.9 ± 1.4	3.6 ± 1.8	3.3 ± 1.9	2.9 ± 1.9	2.2 ± 1.1	0.007

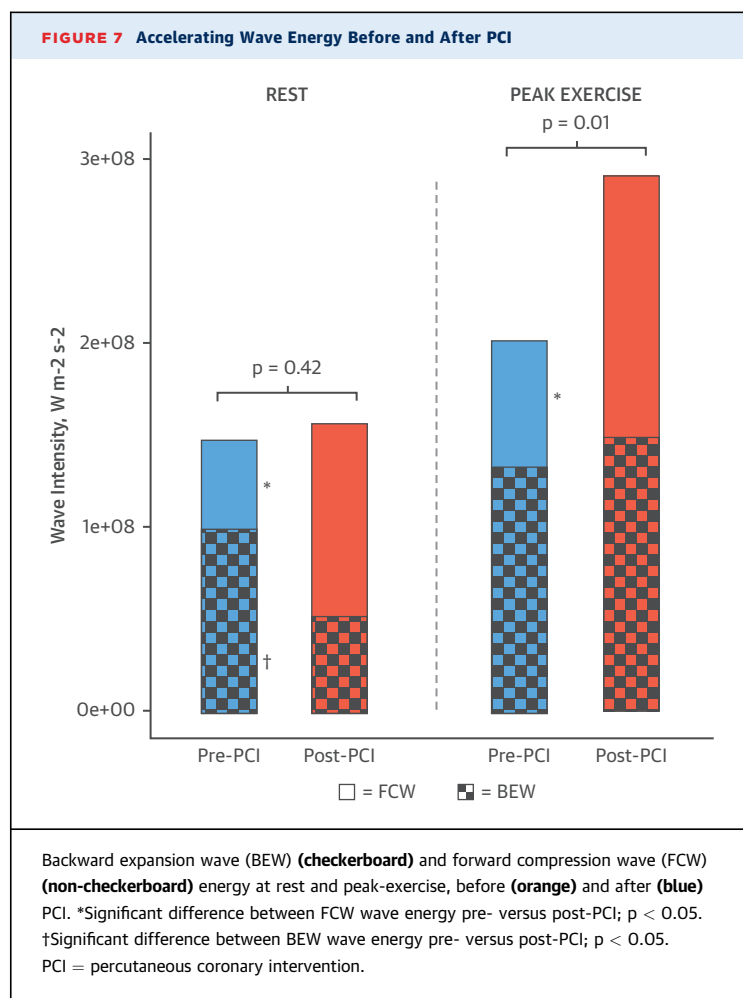
Values are mean ± SD.

ANOVA = analysis of variance; APV = average peak coronary flow velocity; DMR = diastolic microvascular resistance; ΔP = pressure-gradient; DTI = diastolic time index; DTF = diastolic time fraction; Expost = post-percutaneous coronary intervention exercise time; Expre = pre-percutaneous coronary intervention exercise time; HR = heart rate; PCI = percutaneous coronary intervention; Pd = distal coronary pressure; PdPa = pressure ratio; PP = pulse pressure; RPP = rate-pressure product; SBP = systemic blood pressure; SR = stenosis resistance; t50 = 50% of the exercise time; TTI = tension-time index.

FIGURE 6 Coronary and Microcirculatory Hemodynamic Responses to Exercise



Coronary flow velocity, stenosis resistance, pressure gradient, pressure ratio (Pd/Pa), distal coronary pressure (Pd), and diastolic microvascular resistance (DMR) responses to exercise, before (blue) and after (orange) PCI. *Significant difference between time-matched exercise stages pre- versus post-PCI; p < 0.05. †Significant difference between peak-exercise pre- versus post-PCI; p < 0.05. PCI = percutaneous coronary intervention.



exercise. Such findings indicate that with a stenosis remaining in situ, the primary adaptive measures to reduce ischemia during repeat exercise are the enhancement of subendocardial perfusion and the down-regulation of myocardial oxygen demand (5). Conversely, in the present study, where PCI was performed, restoration of normal coronary blood flow during exercise was the overwhelming therapeutic hemodynamic alteration. Accordingly, within our study, transmural redistribution of perfusion was not observed on repeat exercise; and an increase rather than decrease in myocardial workload was demonstrated.

PCI AND CHANGES IN CORONARY-CARDIAC INTERACTION DURING EXERCISE. Coronary WIA permits additional insights into coronary blood flow dynamics during exercise by accounting for the influence of extravascular forces on flow (19). The 2 waves that accelerate flow are the backward expansion wave that occurs in diastole, and the forward

compression wave that occurs in systole (8). It has previously been reported that these 2 waves contribute over 90% of the energy accelerating coronary blood flow (8).

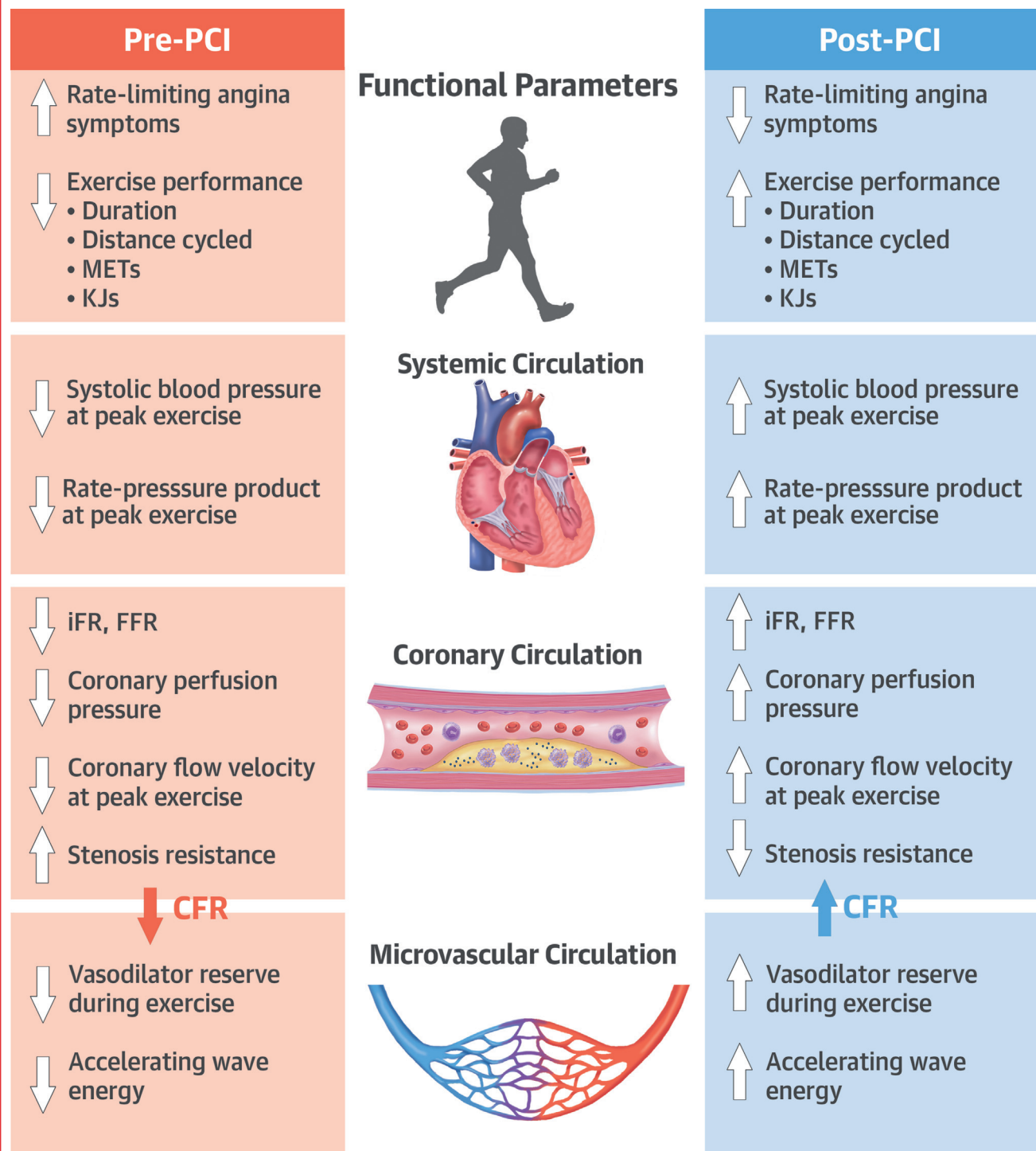
Pre-PCI in the resting state, the BEW was the major contributor to total accelerating wave energy. Although speculative, this finding may be explained by the same coronary autoregulatory process that resulted in a lower diastolic myocardial resistance at rest. When resistance is low, diastolic suction forces are high and the BEW is increased. Conversely, post-PCI in the resting state, the FCW contributed more to total accelerating wave energy at rest. This may be the result of both a higher DMR at rest (and thus lessened diastolic suction) coupled with more effective transmission of left ventricular systolic accelerating forces into the coronary circulation following PCI.

At peak exercise, total accelerating wave energy was higher following PCI than before. The absolute magnitude of BEW energy was similar at peak exercise both before and after PCI. Again, although speculative, this finding may be attributed to the similar minimal diastolic microvascular resistance values (and thus, similar maximal degree of microvascular suction) that were observed. The absolute magnitude of FCW energy was higher at peak exercise after versus before PCI. This is suggestive that the increase in peak exercise total accelerating wave energy post-PCI may be the result of more effective transmission of ventricular originating systolic forces into the coronary circulation during exercise.

CLINICAL IMPLICATIONS. These data demonstrate that PCI immediately normalizes the physiological response to exercise in coronary, microcirculatory, and systemic circulations. These beneficial adaptations were associated with a large improvement in patient symptoms and exercise tolerance; however, the patient was unblinded to the fact they had received PCI. Although this is analogous with everyday clinical practice (i.e., every patient is aware they have received a stent), the results of the recently reported ORBITA trial clearly indicate that there is also a placebo effect associated with undergoing PCI.

As clinicians, we should feel confident about the biological plausibility of PCI as an effective therapy for the relief of angina; however, we should also be aware that patients also gain some functional improvement from placebo. Therefore, we should take the opportunity of the PCI procedure to emphasize to the patient how effective the PCI has been, both anatomically and physiologically. Such

CENTRAL ILLUSTRATION Invasive Exercise Hemodynamics Before and After PCI



Cook, C.M. et al. J Am Coll Cardiol. 2018;72(9):970-83.

CFR = coronary flow reserve; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; METs = metabolic equivalents; PCI = percutaneous coronary intervention.

steps are already commonly performed by some operators (for example, by showing the patient the pre- and post-PCI angiogram images as a demonstration of the anatomic success of the procedure). We speculate that in addition to enhancing overall patient education, simple steps such as these would maximize the overall therapeutic benefit of PCI in stable angina.

STUDY LIMITATIONS. This study addressed only single-vessel disease and only cases with sufficiently focal lesions that there was good expectation of full resolution by stenting. Accordingly, this represents a highly selected group of patients. General clinical practice covers a much wider variety of disease anatomy. It is not known how multivessel disease or multivessel PCI might fair in such a study. The advantage of discrete single-vessel disease is that the anatomy and physiology have a good chance of being normalized by the PCI.

Our study only enrolled patients who would be able to exercise on a supine bicycle. This meant that more frail individuals were not eligible. It also meant that if the operator needed to carry out femoral access, the patient could not conduct the protocol. Furthermore, owing to the potential for (unmeasured) myocardial stunning or hibernation immediately post-PCI, the improvement in functional capacity demonstrated in our study may be an underestimation of the longer-term therapeutic effect.

This multicenter study was designed to detect physiological changes as continuous variables and not count events as binary digits. By collecting more items of information per patient, the number of patients needed to answer a question is smaller in this type of study than in event-counting studies. However, owing to the relatively small number of patients, we may be statistically underpowered to address additional questions such as whether the improvement in functional capacity was significantly greater in LAD versus non-LAD territories ([Online Figure 3](#)).

All our patients received intracoronary nitroglycerin before diagnostic angiography and all physiological measurements. Intracoronary nitroglycerin was necessary to stabilize epicardial tone during physiological assessment and also to ensure accurate vessel sizing in preparation for PCI. We do not know what the results would have been if they had not had this.

We did not measure reproducibility of supine exercise in our patients. This was in order to minimize the burden on patients participating in the study, as

well as the significant time burden imposed on busy clinical catheter laboratory lists. Our reason to believe that the supine exercise test might have satisfactory reproducibility is that before this study began, we ran a pilot study of paired supine exercise tests 30 min apart with healthy controls who were blinded to time during exercise. This pilot phase suggested satisfactory reproducibility, with mean difference of just -6.9 s and a standard deviation of difference of 32 s ([Online Figure 4](#)).

Consistent with real-world clinical practice, this study did not blind patients to the presence of PCI. Accordingly, blinding of exercise testing to time (i.e., pre-PCI versus post-PCI) was absent. Therefore, we must bear in mind that any subjectively reported reduction in symptoms and objectively observed increase in exercise capacity is mediated by a combination of the physical and psychological effects of PCI, the latter of which may be particularly prone to bias. The reason that we did not blind patients in this study is that the blinding protocol in ORBITA (which was enrolling concurrently) necessitated sedation for allocation concealment, and this would have impaired exercise performance.

Lastly, this study did not include a control group of patients (i.e., those who exercised twice, but without intervening PCI). A study of this kind has previously been performed by Lockie et al. ([5](#)) in their investigation of the warm-up angina phenomenon. Accordingly, the hemodynamic and functional improvements observed post-PCI in the present study may also be inclusive of an unmeasured warm-up effect.

CONCLUSIONS

Examining solely objective physiological measures during physical exercise, PCI for single-vessel SCD shows clear evidence of meeting all that could be demanded of a therapy for ischemia. There is immediate normalization of the pattern of exercise-induced changes; in coronary pressure, flow, resistance, and wave intensity; in systemic blood pressure, heart rate, and RPP; and in the microcirculatory vasodilator reserve to physical exercise.

ADDRESS FOR CORRESPONDENCE: Dr. Justin E. Davies, The Hammersmith Hospital, B block South, 2nd floor, NHLI Cardiovascular Science, Du Cane Road, London W12 0NN, United Kingdom. E-mail: drjustindavies@googlemail.com. Twitter: [@imperialcollege](#), [@ImperialNHS](#).

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with stable single-vessel coronary disease, PCI reduces ischemia and restores a normal hemodynamic response to exercise.

TRANSLATIONAL OUTLOOK: Future controlled experimental studies should assess the impact of percutaneous revascularization on exercise hemodynamics in patients with other patterns of ischemic heart disease.

REFERENCES

1. Al-Lamee R, Thompson D, Dehbi H-M, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31-40.
2. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Engl J Med* 1992;326:10-6.
3. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 2008;359:677-87.
4. Wijeyesundera HC, Nallamothu BK, Krumholz HM, Tu JV, Ko DT. Meta-analysis: effects of percutaneous coronary intervention versus medical therapy on angina relief. *Ann Intern Med* 2010;152:370-9.
5. Lockie TPE, Rolandi MC, Guilcher A, et al. Synergistic adaptations to exercise in the systemic and coronary circulations that underlie the warm-up angina phenomenon. *Circulation* 2012;126:2565-74.
6. Lumley M, Williams R, Asress KN, et al. Coronary physiology during exercise and vasodilation in the healthy heart and in severe aortic stenosis. *J Am Coll Cardiol* 2016;68:688-97.
7. Asress KN, Williams R, Lockie T, et al. Physiology of angina and its alleviation with nitroglycerin: insights from invasive catheter laboratory measurements during exercise. *Circulation* 2017;136:24-34.
8. Davies JE, Whinnett ZI, Francis DP, et al. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation* 2006;113:1768-78.
9. Sarnoff SJ, Braunwald E, Welch GH, Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 1958;192:148-56.
10. Buckberg GD, Fixler DE, Archie JP, Hoffman JIE. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res* 1972;30:67-81.
11. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978;57:549-56.
12. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* 2012;59:1392-402.
13. Feigl EO. Coronary physiology. *Physiol Rev* 1983;63:1-205.
14. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev* 2008;88:1009-86.
15. Jayaweera AR, Wei K, Coggins M, Bin JP, Goodman C, Kaul S. Role of capillaries in determining CBF reserve: new insights using myocardial contrast echocardiography. *Am J Physiol* 1999;277:H2363-72.
16. Ball RM, Bache RJ, Cobb FR, Greenfield JC. Regional myocardial blood flow during graded treadmill exercise in the dog. *J Clin Invest* 1975;55:43-9.
17. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res* 1978;43:242-53.
18. Nijjer SS, de Waard GA, Sen S, et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. *Eur Heart J* 2016;37:2069-80.
19. Sun YH, Anderson TJ, Parker KH, Tyberg JV. Wave-intensity analysis: a new approach to coronary hemodynamics. *J Appl Physiol* (1985) 2000;89:1636-44.

KEY WORDS coronary physiology, exercise, percutaneous coronary intervention, stable coronary disease

APPENDIX For supplemental figures and e-mail addresses of the authors, please see the online version of this paper.