Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Methods

The patient was positioned on the catheterization laboratory table and secured to a premounted supine cycle ergometer (Lode Angio, Lode, Groningen; eFigure 1). The ergometer was connected to a laptop computer with software (Lode Export Manager 10, V 10.5.1, Lode, Groningen) to initiate the exercise protocol and acquire performance data. The target-vessel was intubated with a standard 6F guide catheter from the right radial artery. Intra-arterial unfractionated heparin (70-100 U/kg) and intracoronary nitroglycerin (300mcg) were given prior to 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-in intracoronary wire (Combowire XT, Volcano Corp, California) connected to a stand-alone console (Combomap, Volcano Corp, California; eFigure 1) was then advanced to the tip of the guiding catheter and the pressure signals normalized. The Combowire tip-mounted sensor was advanced distal to the stenosis by a minimum of 15mm and its position recorded cineographically. An optimal Doppler velocity trace was obtained by rotational manipulation of the Combowire. Continuous pressure-flow measurements were performed under resting conditions, during a 2-minute 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.

Prior to removal from the patient, the Combowire was returned to the catheter tip to assess for pressure drift. Stenting was then performed according to standard clinical practice. Stent optimization was performed at the operator’s discretion. Following stenting, the Combowire was reintroduced, advanced to the guiding catheter tip and renormalized as before. The Combowire 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. Schematic representation of the study protocol is summarized in eFigure 1.

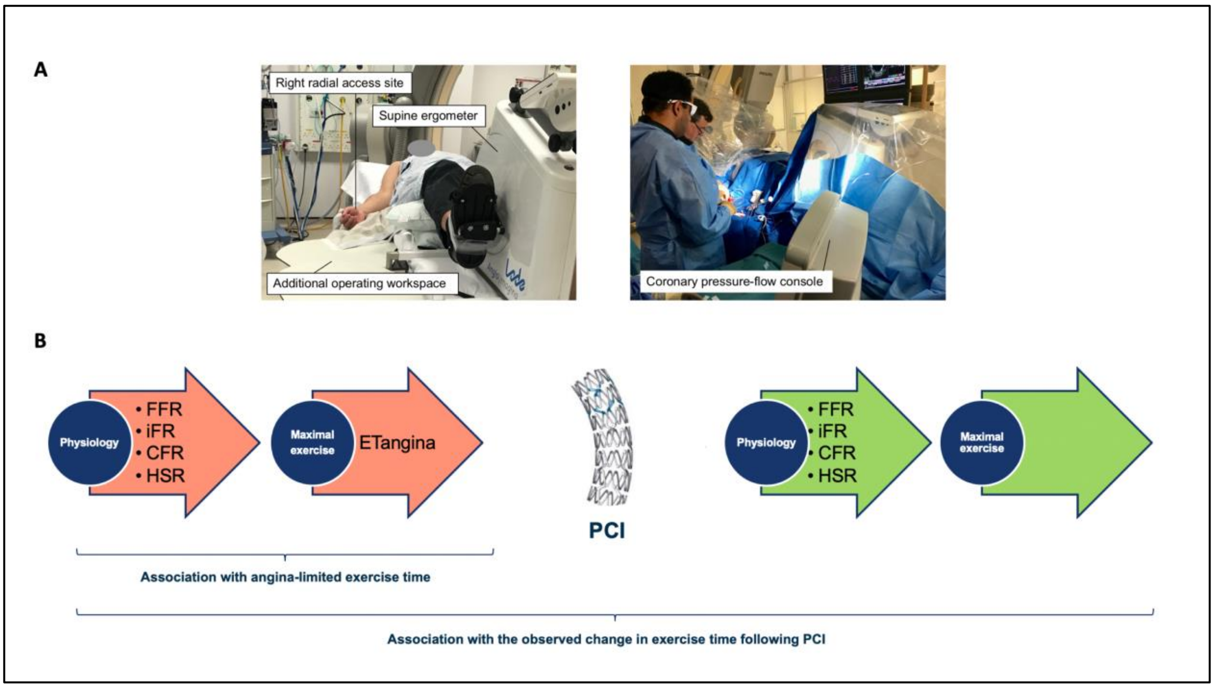
Exercise protocol

An incremental exercise protocol starting at 40 Watts and increasing by 20 Watts 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 (pre-PCI) or physical exhaustion (post-PCI).

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) for offline analysis. Exercise data were exported from the ergometer software package using a dedicated export manager (Lode Export Manager 10, V 10.5.1, Lode, Groningen).

eFigure 1



eFigure 1. Experimental apparatus and study protocol

(A): Experimental apparatus and coronary catheter laboratory set up. (B): Schematic representation of the study protocol.

eTable 1. Calculation of physiologic indices

Pa	=	Proximal (aortic) pressure (mmHg)
Pd	=	Distal (coronary) pressure (mmHg)
FFR	=	Pd/Pa at whole-cycle during pharmacological hyperemia
iFR	=	Pd/Pa at baseline over iFR window
HSR	=	Pa-Pd (mmHg) / Whole - cycle hyperemic flow velocity (cm/s)
CFR	=	Whole-cycle hyperemic flow velocity / Whole-cycle baseline flow velocity

Pa indicates aortic pressure; Pd, distal coronary pressure; FFR, fractional flow reserve; iFR, instantaneous wave-Free Ratio; HSR, hyperemic stenosis resistance; CFR, coronary flow reserve

eTable 2. Baseline characteristics

Demographics (n=23)	
Age (years)	60.6 (8.1)
Male	21 (91%)
Diabetes	1 (4%)
Hypertension	14 (61%)
Hyperlipidaemia	16 (70%)
History of smoking	9 (39%)
Previous myocardial infarction	3 (13%)
LVEF < 40%	0 (0%)
CCS class	
I	1 (4%)
II	9 (39%)
III	13 (57%)
Baseline hemodynamics	
Systolic blood pressure (mmHg)	140 (18)
Heart rate (bpm)	68 (12)
Medications	
Aspirin	23 (100%)
Clopidogrel	23 (100%)
Beta-blockers	16 (70%)
Statin	22 (96%)
ACE-I/ARB	17 (74%)
Nitrates	6 (26%)
CCB	9 (39%)

PCI indicates percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society; bpm, beats per minute; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

eTable 3. Per vessel anatomical and physiological stenosis characteristics

Vessel	Proximal stenosis location	Diameter stenosis by QCA	FFR pre-PCI	iFR pre-PCI	HSR pre-PCI	CFR pre-PCI	FFR post-PCI	iFR post-PCI	HSR post-PCI	CFR post-PCI	∆FFR	∆iFR	∆HSR	∆CFR
LAD	64% (9/14)	72.2% (11.3)	0.50 (0.43-0.73)	0.49 (0.33-0.87)	1.65 (0.79-3.38)	1.43 (1.11-2.29)	0.89 (0.84-0.91)	0.94 (0.93-0.98)	0.27 (0.13-0.38)	2.73 (2.28-3.12)	0.32 (0.18-0.42)	0.33 (0.09-0.57)	-0.87 (-2.38- -0.44)	1.41 (0.75-1.50)
Cx	80% (4/5)	74.5% (5.8)	0.64 (0.54-0.80)	0.79 (0.49-0.87)	1.22 (0.84-1.61)	2.12 (1.30-2.15)	0.97 (0.93-1.01)	1.00 (0.98-1.01)	0.04 (0.00-0.25)	2.77 (2.58-3.20)	0.29 (0.20-0.37)	0.14 (0.06-0.28)	-0.95 (-2.70- -0.55)	0.70 (0.44-1.19)
RCA	0% 0/4	84.5% (7.3)	0.43 (0.29-0.60)	0.61 (0.40-0.78)	2.95 (1.88-5.27)	1.23 (1.08-1.36)	0.96 (0.94-0.97)	1.00 (0.98-1.01)	0.10 (0.09-0.11)	2.73 (2.50-3.04)	0.49 (0.36-0.62)	0.37 (0.23-0.56)	-2.81 (-5.13- -1.78)	1.51 (1.14-1.96)

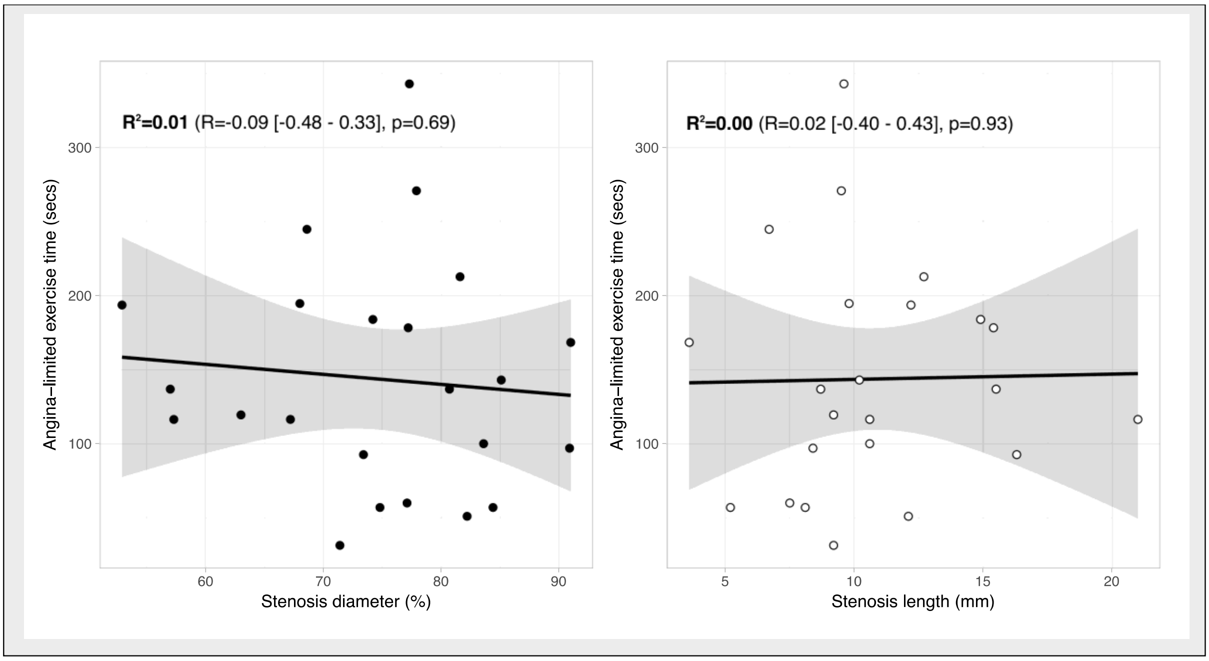
Values are n, mean ± SD, median (IQR) or n (%). LAD indicates left anterior descending; Cx, circumflex; RCA, right coronary artery; QCA, quantitative coronary angiography.

eTable 4. Univariate linear regression of baseline characteristics and anatomical stenosis characteristics on angina-limited exercise time.

Univariate predictors of ET_{angina}			
Variable	β coefficient	95% CI	p value
Patient characteristics			
Age	-2.27	-6.5 – 1.94	0.27
Male	32.3	-88.5 – 153	0.58
Diabetes	-48.8	-215 – 118	0.55
Hypertension	-24.8	-94.1 – 44.6	0.47
Hyperlipidaemia	-19.3	-93.3 – 54.7	0.59
History of smoking	-13.4	-83.4 – 56.6	0.70
Previous myocardial infarction	-62.1	-160 – 35.8	0.21
Number of antianginal medications	-3.84	-59.2 – 51.5	0.89
Anatomical stenosis characteristics			
Reference vessel diameter (mm)	3.93	-76.0 – 83.9	0.92
Stenosis diameter (%)	-0.68	-4.05 – 2.70	0.68
Stenosis length (mm)	0.93	-8.56 – 9.28	0.93
Physiological stenosis characteristics			
FFR	226	59.5 – 393	0.01
iFR	198	97.2 – 299	<0.001
Log HSR	-122	-191 – -52.2	<0.01
CFR	44.7	0.21 – 91.7	0.05

ET_{angina} indicates the change in exercise time following PCI. All abbreviations as per eTable 1

eFigure 2



eFigure 2. The relationship between angina-limited exercise time and anatomical stenosis severity

Scatter plots of the relationships between angina-limited exercise time and percentage stenosis diameter (black) and stenosis length in millimetres (white).