Comparing invasive hemodynamic responses in adenosine hyperemia versus physical exercise stress in chronic coronary syndromes

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What is already known about this subject?
Adenosine hyperemia leads to vasodilatation of the coronary microcirculation and stabilization of microvascular resistance. This in turn permits the use of hyperemic coronary pressure ratios to quantify the flow-limiting potential of a coronary stenosis (i.e. the Fractional Flow Reserve).

What does this study add?
In patients with chronic coronary syndrome (CCS) and coronary stenosis, invasive hemodynamic responses differed markedly between adenosine hyperemia versus physical exercise stress. These differences were observed across systemic, coronary and microcirculatory hemodynamics.

How might this impact on clinical practice?
Adenosine hyperemia is a validated and integral component of functional myocardial ischemia assessment, both invasively and non-invasively. However, the findings of the present study (as well as previous studies) remind the clinician that the physiological and hemodynamic responses to adenosine hyperemia cannot be considered as directly comparable to those of physical exercise.

Structured Abstract

Objectives: Adenosine hyperemia is an integral component of the physiological assessment of obstructive coronary artery disease in patients with chronic coronary syndrome (CCS). The aim of this study was to compare systemic, coronary and microcirculatory hemodynamics between intravenous (IV) adenosine hyperemia versus physical exercise stress in patients with CCS and coronary stenosis.

Methods: Twenty-three patients (mean age, 60.6±8.1 years) with CCS and single-vessel coronary stenosis underwent cardiac catheterization. Continuous trans-stenotic coronary pressure-flow measurements were performed during: i) IV adenosine hyperemia, and ii) physical exercise using a catheter-table-mounted supine ergometer. Systemic, coronary and microcirculatory hemodynamic responses were compared between IV adenosine and exercise stimuli.

Results: Mean stenosis diameter was 74.6%±10.4. Median (interquartile range) FFR was 0.54 (0.44-0.72). At adenosine hyperemia versus exercise stress, mean aortic pressure (Pa, 91±16 mmHg vs 99±15 mmHg, p<0.0001), distal coronary pressure (Pd, 58±21 mmHg vs 69±24 mmHg, p<0.0001), trans-stenotic pressure ratio (Pd/Pa, 0.63±0.18 vs 0.69±0.19, p<0.0001), microvascular resistance (MR, 2.9±2.2 mmHg.cm-1.sec-1 vs 4.2±1.7 mmHg.cm-1.sec-1, p=0.001), heart rate (HR, 80±15 bpm vs 85±21 bpm, p=0.02) and rate-pressure product (RPP, 7522±2335 vs 9077±3200, p=0.0001) were all lower. Conversely, coronary flow velocity (APV, 23.7±9.5 cm/s vs 18.5±6.8 cm/s, p=0.02) was higher. Additionally, temporal changes in Pa, Pd, Pd/Pa, MR, HR, RPP and APV during IV adenosine hyperemia versus exercise were all significantly different (p<0.05 for all).

Conclusions: In patients with CCS and coronary stenosis, invasive hemodynamic responses differed markedly between IV adenosine hyperemia versus physical exercise stress. These differences were observed across systemic, coronary and microcirculatory hemodynamics.

248/250

Key words

Coronary physiology
Exercise physiology
Chronic coronary syndromes
Coronary artery disease

Introduction

Adenosine is a naturally occurring vasodilator with an essential role in the autoregulation of coronary blood flow [1]. Administration of adenosine leads to stabilization and minimization of coronary microvascular resistance and a resultant increase in coronary flow – a process termed adenosine hyperemia [2,3]. Accordingly, in both invasive and non-invasive settings, adenosine hyperemia is utilized for the functional assessment of patients with chronic coronary syndrome (CCS) and coronary stenosis. Within the cardiac catheter laboratory, adenosine hyperemia is an integral component of invasive Fractional Flow Reserve (FFR) assessment - a coronary pressure-derived estimate of coronary blood flow impairment in patients with CCS.

Despite the common-place use of adenosine, precise and contemporary comparisons of the invasive physiological responses to adenosine hyperemia versus physical exercise stress in patients with chronic coronary syndromes (CCS) and coronary stenosis are lacking. Previously, we reported a study that utilized supine exercise during invasive coronary catheterization to comprehensively investigate exercise hemodynamics in patients with CCS [4]. In the present study we perform a separate analysis to comparatively assess invasive systemic, coronary and microcirculatory hemodynamics in patients with CCS and coronary stenosis during IV adenosine hyperemia versus physical exercise stress.

Methods

Study population

Patients were recruited from elective coronary angioplasty waiting lists at both the Essex Cardiothoracic Centre and the Hammersmith Hospital, United Kingdom. Inclusion criteria were single-vessel coronary artery disease and exercise capacity limited by angina (confirmed during the exercise stage of the study protocol). Exclusion criteria were multi-vessel coronary artery disease, left main stem or ostial stenosis, left ventricular ejection fraction <40%, moderate/severe valvular disease, chronotropic incompetence with pacemaker, severe airways disease, physical inability to exercise or exercise capacity not limited by angina. Patients continued all their usual medications and were loaded with dual antiplatelets as per routine practice of the recruiting centre. All subjects gave written consent in accordance with the protocol approved by the regional ethics committee (16/LO/1928).

Catheterization and exercise protocol

The patient was positioned on the coronary catheterization laboratory table and secured to a pre-mounted supine cycle ergometer (Lode Angio, Lode, Groningen). 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 exercise 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 all physiological measurements.

A standard coronary guidewire was first advanced distal to the stenosis to secure the target vessel. A dual pressure and velocity sensor 0.014-in intracoronary wire (Combowire XT, Volcano Corp, California) 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. Continuous pressure-flow measurements were performed under resting conditions, at peak hyperemia during a 2-minute peripheral intravenous (IV) infusion of adenosine and throughout the duration of exercise. All patients exercised on an incremental exercise protocol starting at 40 Watts and increasing by 20 Watts every minute. Patients exercised until the development of angina (defined as chest pain or rate-limiting shortness of breath). The order of adenosine hyperemia and physical exercise stress was randomised. Prior to removal from the patient, the Combowire was returned to the catheter tip to assess for pressure drift.

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).

Statistical analysis

Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were expressed as mean (± standard deviation) or median (interquartile range [IQR]), as

appropriate. Categorical variables were expressed as numbers and percentages. Continuous variables were compared with paired t-tests. Repeated measures ANOVA was used to evaluate trends across the stages of adenosine versus exercise stress. 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-three patients (21 male; age, 60.6 ± 8.1 years) completed the study protocol. The baseline characteristics of the study population are summarised in Table 1. The majority (96%) of patients were in Canadian Cardiovascular Society class 2 or 3 at enrolment. The mean number of prescribed antianginal medications per patient was 1.4 ± 0.7.

Stenosis and procedural characteristics

All stenoses were focal and predominantly proximal (57% [13/23]). The most frequently assessed vessel was the left anterior descending (LAD) artery (52% [12/23]). Stenoses were anatomically and physiologically severe. Mean stenosis diameter by quantitative coronary angiography was 74.6% ± 10.4. Median (interquartile range) FFR, whole-cycle Pd/Pa and iFR were 0.54 (0.44 to 0.72), 0.70 (0.54 to 0.90) and 0.53 (0.35 to 0.83), respectively. Full anatomical and physiological stenosis characteristics are shown in Table 2.

Intravenous adenosine and exercise stress characteristics

Steady-state hyperemia was achieved in all patients within two minutes of IV adenosine infusion. Exercise stress was determined symptomatically, with all patients stopping exercise because of angina-like symptoms. Mean exercise time, peak metabolic equivalents (METs), peak Watts and total energy expenditure were 144 ± 77 seconds, 4.3 ± 1.2 METs, 85 ± 30 Watts and 7.8 ± 7.0 KJ, respectively.

Systemic hemodynamic responses

Systemic hemodynamic responses at IV adenosine hyperemia versus exercise stress are displayed in Figure 1A. Mean aortic pressure (91 ± 16 mmHg vs 99 ± 15 mmHg, $p<0.0001$), heart rate (80 ± 15 bpm vs 85 ± 21 bpm, $p=0.02$) and rate-pressure product (7522 ± 2335 vs 9077 ± 3200, $p=0.0001$) were all significantly lower at adenosine versus exercise stress.

Temporal changes in systemic hemodynamics during IV adenosine and exercise are displayed in Figure 1B. The most marked difference was observed in the mean aortic blood pressure response to adenosine versus exercise ($p<0.0001$). During adenosine infusion there was a progressive decline in Pa pressure towards adenosine stress. Conversely, during exercise, there was an initial increase in mean aortic blood pressure followed by a subsequent decline at exercise stress, coinciding with the onset of rate-limiting angina symptoms. Heart rate and rate-pressure product increased during both IV adenosine and exercise, however, the patterns of increase were significantly different during adenosine versus exercise ($p<0.001$ for HR and $p<0.0001$ for RPP).

Coronary hemodynamic responses

Coronary hemodynamic responses at IV adenosine hyperemia versus exercise stress are displayed in Figure 2A. Coronary flow velocity (average peak velocity (APV), 24 ± 10 vs 19 ± 7 cm/s, p=0.02) and the trans-stenotic pressure drop (ΔP, 33 ± 15 vs 29 ± 18 mmHg, p=0.01) were significantly higher at adenosine hyperemia versus exercise stress. Conversely, distal coronary pressure (Pd, 58 ± 21 vs 69 ± 24 mmHg, p<0.0001) and trans-stenotic pressure ratio (Pd/Pa, 0.63 ± 0.18 vs 0.69 ± 0.19, p<0.0001) were significantly lower at IV adenosine hyperemia versus exercise stress. Only stenosis resistance was similar between the two stimuli (SR, 1.8 ± 1.6 vs 1.9 ± 2.1 $mmHg.cm^{-1}.sec^{-1}$, p=0.81).

Temporal changes in coronary hemodynamics during IV adenosine hyperemia and exercise stress are displayed in Figure 2B. During adenosine infusion there was a progressive increase in coronary flow velocity towards adenosine hyperemia. During exercise stress coronary flow velocity increased differently, plateauing earlier and at a lower value than during adenosine stress (p=0.03).

Consequent to the larger rise in coronary flow velocity with adenosine, the trans-stenotic pressure drop was greater (p=0.002) and the distal coronary pressure (p<0.0001) and trans-stenotic ratio lower (p<0.0001) throughout adenosine compared to exercise stress. Stenosis resistance remained similarly constant throughout both stimuli (p=0.34).

Microvascular hemodynamic responses

Microvascular hemodynamics at IV adenosine hyperemia versus exercise stress are displayed in Figure 3A. Microvascular resistance (MR, 2.9 ± 2.2 vs 4.2 ± 1.7 $mmHg.cm^{-1}.sec^{-1}$, p=0.001) was significantly lower at adenosine hyperemia versus exercise stress. The pattern

of decline in microvascular resistance with adenosine and exercise was also markedly different (Figure 3B, $p<0.0001$). During adenosine infusion microvascular resistance decreased profoundly and early. In contrast, during exercise, microvascular resistance decreased gradually and reached a higher nadir value at peak exercise stress. Full numerical comparison of systemic, coronary and microvascular hemodynamic responses to IV adenosine hyperemia versus exercise stress are displayed in Table 3.

Discussion

The current study sought to compare the precise invasive hemodynamic responses to IV adenosine hyperemia versus physical exercise stress in patients with chronic coronary syndrome and coronary stenosis. The main findings of this study were as follows.

First, systemic hemodynamic responses were different between IV adenosine hyperemia and exercise stress. Specifically, mean aortic blood pressure (Pa), heart rate and myocardial workload (RPP) were lower at adenosine versus exercise stress. Second, coronary hemodynamic responses were different between IV adenosine hyperemia and exercise stress. Specifically, distal coronary pressure (Pd), trans-stenotic pressure drop (ΔP) and trans-stenotic pressure ratio (Pd/Pa) were lower, and coronary flow velocity (APV) higher, during IV adenosine versus exercise stress. Last, systemic hemodynamic responses were different between adenosine hyperemia and exercise stress. Specifically, microvascular resistance (MR) was lower during IV adenosine versus exercise. In summary, in patients with CCS and coronary stenosis, compared to physical exercise stress, IV adenosine hyperemia elicited a markedly different physiological response in systemic, coronary and microcirculatory hemodynamics (Figure 4).

Adenosine hyperemia

Adenosine is a naturally occurring nucleoside base of both adenosine triphosphate (ATP) and the signalling molecule cyclic adenosine monophosphate (cAMP) [5]. Within the coronary circulation, adenosine exerts its pharmacologic effect primarily on the A2A receptor (A2AR) [6]. Activation of this receptor produces vasodilatation of the coronary microcirculation,

leading to a fall in microvascular resistance and a resultant increase in coronary blood flood [2,3].

Physiological mechanisms of adenosine hyperemia versus physical exercise stress

Physical exercise is considered the most important physiological stimulus for increased myocardial oxygen demand [7]. In health, the principal mechanism of supporting cardiac responses to exercise is via augmentation of coronary blood flow, itself a result of a reduction in coronary vascular resistance. This ability to regulate coronary vasomotor tone in response to exercise is the result of the interplay between a multitude of vasodilator and vasoconstrictors influences (as well as neurohormonal, endothelial and myocardial factors) [7]. Exercise is characterised by a reduction in cardiac parasympathetic activity and, conversely, an increase in sympathetic activity. Together, these autonomic influences increase heart rate, stroke volume and cardiac output, thereby facilitating the redistribution of blood flow to skeletal muscle groups [8].

Within our study, despite exercising our CCS patients to the onset of rate-limiting angina, IV adenosine hyperemia was associated with an additional increase in coronary flow (and reduction in microvascular tone), seemingly in contrast to the traditional view that myocardial ischemia causes maximal microvascular dilation [7]. In fact, this finding is in keeping with the concept of Fenouillet et al. [9] who described the existence of adenosine ‘receptor reserve’, also known as ‘spare receptors’, in coronary artery disease (CAD) patients. Within this model, spare receptors are associated with the presence of inducible ischemia, with the presence of spare receptors occurring because of the internalisation of A2AR [10]. Subsequently, A2AR oligomerized in order to obtain the full effect when a

single receptor is occupied within oligomers, thereby leaving a reserve according to the revisited spare receptor theory for unconventional coupling of receptor and effector [11]. However, in inducible ischemia, insufficient A2AR oligomers are expressed on the cell surface in order to produce effective vasodilation [12]. These observations support the earlier findings of Nishimura et al [13], who in their study compared the localisation and quantification of perfusion defects noninvasively by thallum-201 single-photon tomography in patients undergoing both intravenous adenosine and physical exercise, assessed 30 days apart. Specifically, Nishimura et al identified that adenosine thallium-201 scintigraphy provided diagnostic information similar to that of exercise scintigraphy, although values for defect sizes were greater with adenosine [13].

Previously, Lumley et al described the changes in coronary blood flow and cardiac-coronary coupling during IV adenosine hyperemia versus exercise stress in healthy subjects, without angina or coronary stenosis [14]. Their findings also demonstrated IV adenosine hyperemia was associated with a larger augmentation in coronary blood flow, a greater reduction in myocardial resistance and a less pronounced increase in heart rate than exercise [14]. Accordingly, the findings of the present study (conducted in patients with CCS and coronary stenosis) are concordant with those of Lumley et al (conducted in healthy subjects); thereby suggesting that the hemodynamic differences between adenosine versus exercise stress are independent of either coronary artery disease or angina symptoms.

Limitations

Within the present study we recruited only patients with severe, single vessel coronary stenosis, the angiographic severity of which are beyond those considered clinically for

physiological assessment. Accordingly, our patients represent a highly selected patient cohort, and different results may have been obtained were we to have included more moderate severity coronary stenoses in our study. Future studies exploring invasive exercise hemodynamics should ideally be focused on more moderate severity coronary lesions. Additionally, we recruited only patients who were physically capable of exercising during their invasive coronary catheterisation procedure. Accordingly, this reflects a selected patient population with a relatively low mean age (60.6 ± 8.1 years), an underrepresentation of female patients (9%) and an absence of diabetes mellitus. Young age [15] and freedom from diabetes [16] have both been associated with coronary microvascular health and thus a more profound hyperemic flow response to adenosine. Accordingly, the adenosine responses observed within our patient cohort may not be fully representative of the broader spectrum of patients with coronary artery disease and angina.

In our study we elected to administer adenosine via intravenous infusion in order to allow for the temporal changes of hemodynamic responses to be recorded. Accordingly, our findings are not translatable to adenosine hyperemia obtained from alternative routes, principally intracoronary adenosine. Additionally, in line with routine clinical practice, patients within our study continued their anti-anginal medications before their invasive procedure. Therefore, the negative inotropic and chronotropic effects of beta-blockers (of which 70% of patients were taking) will have blunted the physiological response to physical exercise. This may have contributed to the relatively low level of exercise achieved in our patient cohort (4.3 ± 1.2 METs, 85 ± 30 Watts and 7.8 ± 7.0 KJ), possibly suggestive of submaximal exercise. However, all patients exercised until the onset of angina-like symptoms. In summary, our findings may not be directly translatable to patients not treated with beta-blocker medications nor patients who achieve true maximal physical exercise.

It is increasingly recognised that myocardial ischemia and angina can exist in the absence of epicardial coronary disease [17] – so-called ischemia and no obstructive coronary artery disease (INOCA). The principle pathophysiological mechanisms responsible for INOCA are impaired microcirculatory conductance and/or arteriolar dysregulation. Because we included only patients with severe, single vessel coronary stenosis, our results are not applicable to the increasingly prevalent cohort of patients with INOCA. However, supine ergometer experiments such as the one conducted in the present study have recently yielded increased insights into the pathophysiology of INOCA [18].

Within the study protocol, administration of intracoronary nitroglycerin was mandated prior to performing all angiography and physiological measurements. This ensured stabilization of epicardial vascular tone and thus the accuracy of trans-stenotic coronary pressure and flow recordings. However, it is well recognised that in a proportion of patients with atherosclerosis, endothelial dysfunction (i.e. paradoxical coronary vasoconstriction) can be a significant contributor to exercise-induced angina symptoms [19]. However, owing to the administration of intracoronary nitroglycerin, any such endothelial dysfunction would have been masked within the current study. Accordingly, the coronary hemodynamic response of our study population may be an overestimation of that experienced under real-world exercise conditions.

Lastly, although a return to baseline heart rate and systolic blood pressure was mandated between adenosine and exercise stress runs, it is conceivable that a warm-up [20] or preconditioning effect [21,22] may have occurred between the two stressor stimuli. To

mitigate this potential confounding influence, the order of exercise and adenosine stress was randomized for each patient.

Conclusions

Intravenous adenosine hyperemia elicited a markedly different physiological response to physical exercise stress in patients with chronic coronary syndrome and coronary stenosis. These differences were seen in the coronary circulation, the microcirculation and systemic hemodynamics.

Contributorship Statement

Christopher M Cook: Guarantor; Data curation; Formal analysis; Investigation; Supervision
James P Howard: Formal analysis; Investigation
Yousif Ahmad: Formal analysis; Investigation
Matthew J Shun-Shin: Formal analysis; Investigation
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Justin E Davies: Guarantor; Supervision; Conceptualization

Abbreviations

CCS	Chronic coronary syndromes
ΔP	Trans-stenotic pressure gradient
FFR	Fractional flow reserve
NHPR	Non hyperemic pressure ratio
MR	Microvascular resistance
Pa	Aortic pressure
Pd	Distal coronary pressure
Pd/Pa	Trans-stenotic pressure ratio
RPP	Rate pressure product
SR	Stenosis resistance

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Competing Interests

JED and JM hold patents pertaining to the iFR technology. JED and AS are consultants for Philips Volcano. RA-L, SS, RP, CC, and SSN have received speaker's honoraria from Philips Volcano. JED and TK have received research grants from Philips Volcano. All other authors declare no competing interests.

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Figure legends

Figure 1: Systemic hemodynamic responses to adenosine hyperemia versus physical exercise stress

(A) Boxplots of systemic hemodynamic responses during adenosine (red) versus exercise (blue). The horizontal black line indicates the mean value. The box indicates the standard deviation and the whiskers indicate the range of values. (B) Temporal trends in systemic hemodynamic responses during adenosine (red) versus exercise (blue) stress. The error bars indicate the standard error. *Significant difference between adenosine versus exercise hemodynamic response, $p<0.05$. Pa indicates mean aortic pressure; HR, heart rate; RPP, rate-pressure product.

Figure 2: Coronary hemodynamic responses to adenosine hyperemia versus physical exercise stress

(A) Boxplots of coronary hemodynamic responses during adenosine (red) versus exercise (blue). (B) Temporal trends in coronary hemodynamic responses during adenosine (red) versus exercise (blue) stress. *Significant difference between adenosine versus exercise hemodynamic response, $p<0.05$. APV indicates average peak coronary flow velocity; ΔP, trans-stenotic pressure drop; Pd, distal coronary pressure; Pd/Pa, trans-stenotic pressure ratio; SR, stenosis resistance.

Figure 3: Microcirculatory hemodynamic response to adenosine hyperemia versus physical exercise stress

(A) Boxplots of the microcirculatory hemodynamic response during adenosine (red) versus exercise (blue) stress. (B) Temporal trends in the microcirculatory hemodynamic response

during adenosine (red) versus exercise (blue) stress. *Significant difference between adenosine versus exercise hemodynamic response, $p<0.05$. MR indicates microvascular resistance.

Figure 4: Summary of the invasive hemodynamic responses to adenosine hyperemia versus physical exercise stress in patients with chronic coronary syndromes and coronary stenosis

Schematic illustration of the comparison between invasive hemodynamic responses to adenosine hyperemia versus physical exercise stress in patients with angina and coronary stenosis. All abbreviations as per previous Figures.

Table 1: Baseline characteristics

Demographics	
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%)
Canadian Cardiovascular Society class	
I	1 (4%)
II	9 (39%)
III	13 (57%)
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%)

LVEF indicates left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Table 2: Anatomical and physiological stenosis characteristics

Target vessel (LAD/Cx/RCA)	14/5/4
Stenosis location (proximal/mid/distal)	13/8/2
Diameter stenosis by QCA	74.46% (10.4)
Stenosis length (mm)	10.7 (3.9)
FFR	0.54 (0.44 - 0.72)
iFR	0.53 (0.35 - 0.83)
Whole-cycle Pd/Pa	0.70 (0.54 - 0.90)

LAD indicates left anterior descending; Cx, circumflex; RCA, right coronary artery; QCA, quantitative coronary angiography; mm, millimetre; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; whole-cycle Pd/Pa, baseline distal-to-aortic pressure ratio.

Table 3: Hemodynamic responses to IV adenosine versus exercise stress

	Adenosine hyperemia				Exercise stress				
Variable	**Baseline**	**1 minute**	**Half maximum**	**Maximum**	**Baseline**	**1 minute**	**Half maximum**	**Maximum**	**p-value (ANOVA)**
Pa (mmHg)	97.1 (11.5)	91.8 (13.2)	91.8 (13.2)	90.7 (15.7)	98.7 (12.1)	105.5 (14.3)	107.1 (14.6)	99.3 (15.1)	<0.0001
HR (bpm)	68.7 (13.0)	76.2 (18.1)	76.2 (18.1)	80.3 (14.6)	72.1 (14.7)	85.2 (13.1)	85.1 (15.9)	84.7 (21.2)	0.0001
RPP (mmHg.bpm)	6913 (1826)	7288 (2370)	7288 (2370)	7522 (2335)	7552 (2153)	8927 (3206)	9250 (3608)	9077 (3201)	<0.0001
APV (cm/s)	16.24 (5.7)	22.6 (9.5)	22.6 (9.5)	23.7 (9.5)	15.3 (4.9)	18.9 (6.1)	19.0 (7.2)	18.5 (6.8)	0.03
ΔP (mmHg)	23.3 (19.8)	32.2 (15.8)	32.2 (15.8)	32.9 (15.4)	25.3 (21.5)	24.0 (18.2)	27.2 (18.4)	28.5 (18.0)	0.002
Pd (mmHg)	73.7 (21.9)	59.8 (17.9)	59.8 (17.9)	57.8 (21.1)	73.3 (23.5)	81.0 (20.4)	79.5 (23.8)	69.4 (23.6)	<0.0001

Pd/Pa	0.76 (0.20)	0.65 (0.17)	0.65 (0.17)	0.63 (0.18)	0.74 (0.21)	0.77 (0.16)	0.74 (0.18)	0.69 (0.19)	<0.0001
SR (mmHg.cm^{-1}.s^{-1})	1.7 (1.8)	1.9 (1.8)	1.9 (1.8)	1.8 (1.6)	2.1 (2.7)	1.6 (1.9)	2.0 (1.7)	1.9 (2.1)	0.34
MR (mmHg.cm^{-1}.s^{-1})	5.0 (2.1)	3.0 (1.5)	3.0 (1.5)	2.5 (1.0)	5.1 (1.9)	4.7 (1.7)	4.5 (1.7)	4.2 (1.7)	<0.0001

Values are mean ± SD. Bpm indicates beats per minute; Pa, mean aortic pressure; HR, heart rate; RPP, rate-pressure product; APV, average peak coronary flow velocity; ΔP, trans-stenotic pressure drop; Pd, distal coronary pressure; PP, pulse pressure; PdPa, trans-stenotic pressure ratio; SR, stenosis resistance; MR, microvascular resistance.

Figures

Figure 1.

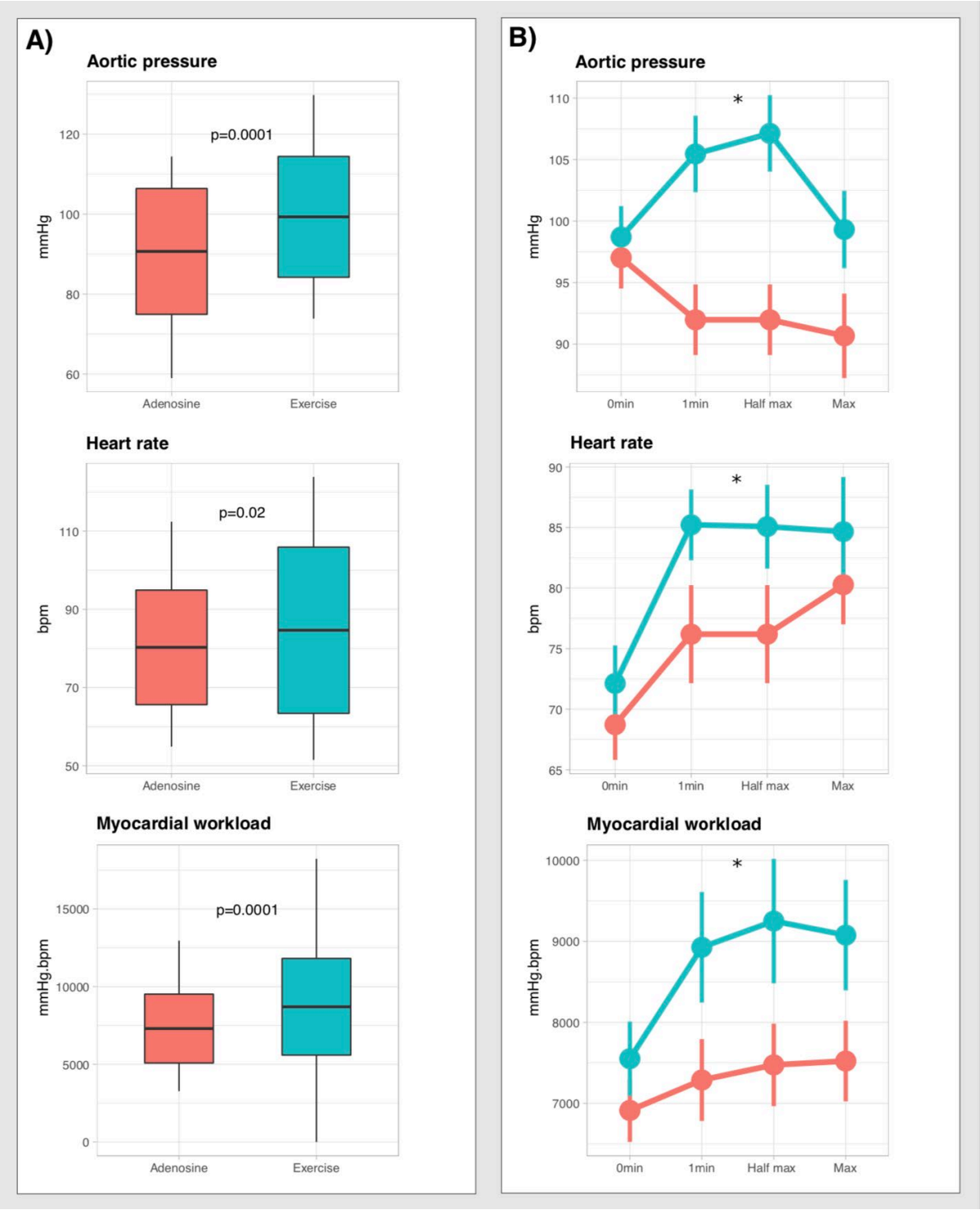


Figure 2.

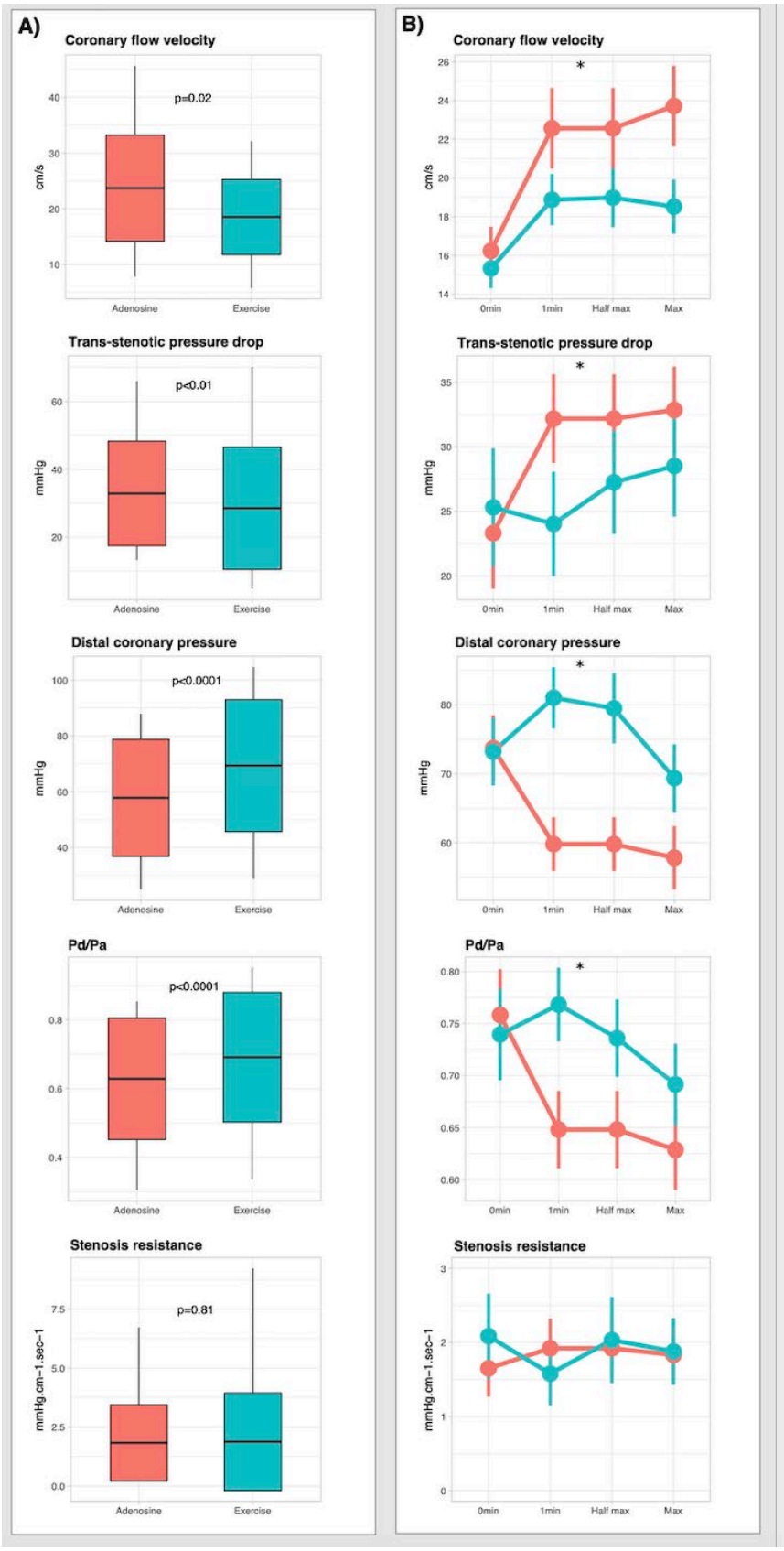

A)
Coronary flow velocity
p=0.02
cm/s
Adenosine
Exercise
Trans-stenotic pressure drop
p<0.01
mmHg
Distal coronary pressure
p<0.0001
Pd/Pa
p<0.0001
Stenosis resistance
p=0.81
mmHg.cm−1.sec−1
B)
Coronary flow velocity
Trans-stenotic pressure drop
Distal coronary pressure
Pd/Pa
Stenosis resistance
0min
1min
Half max
Max

Figure 3.

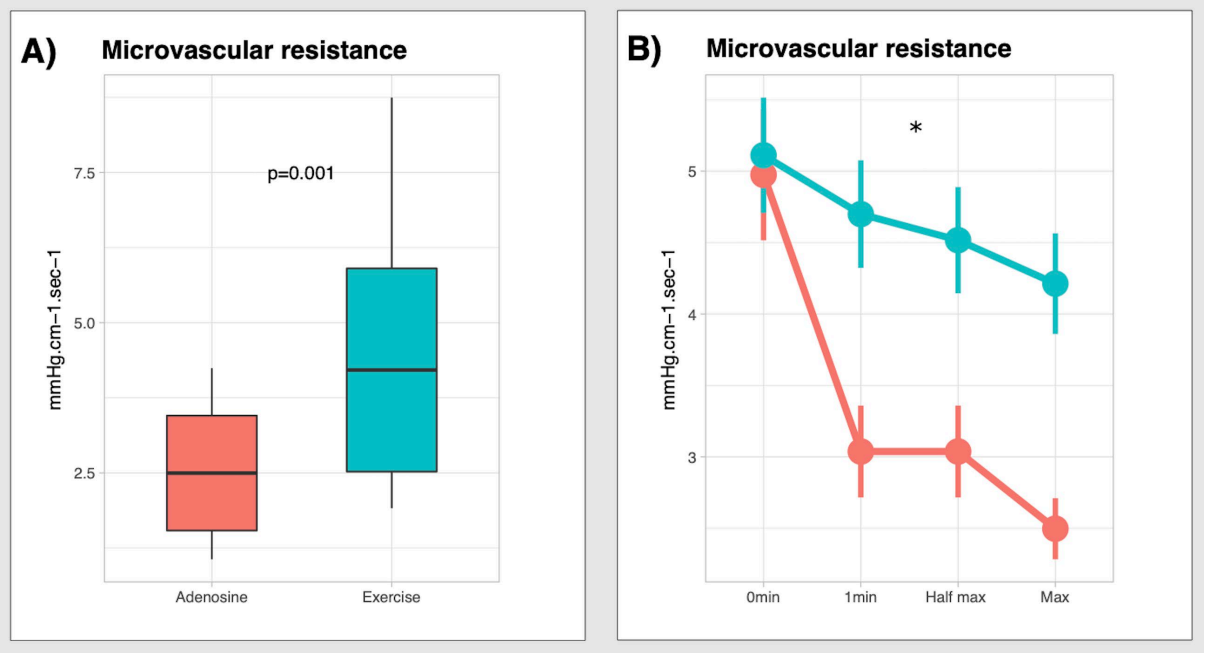
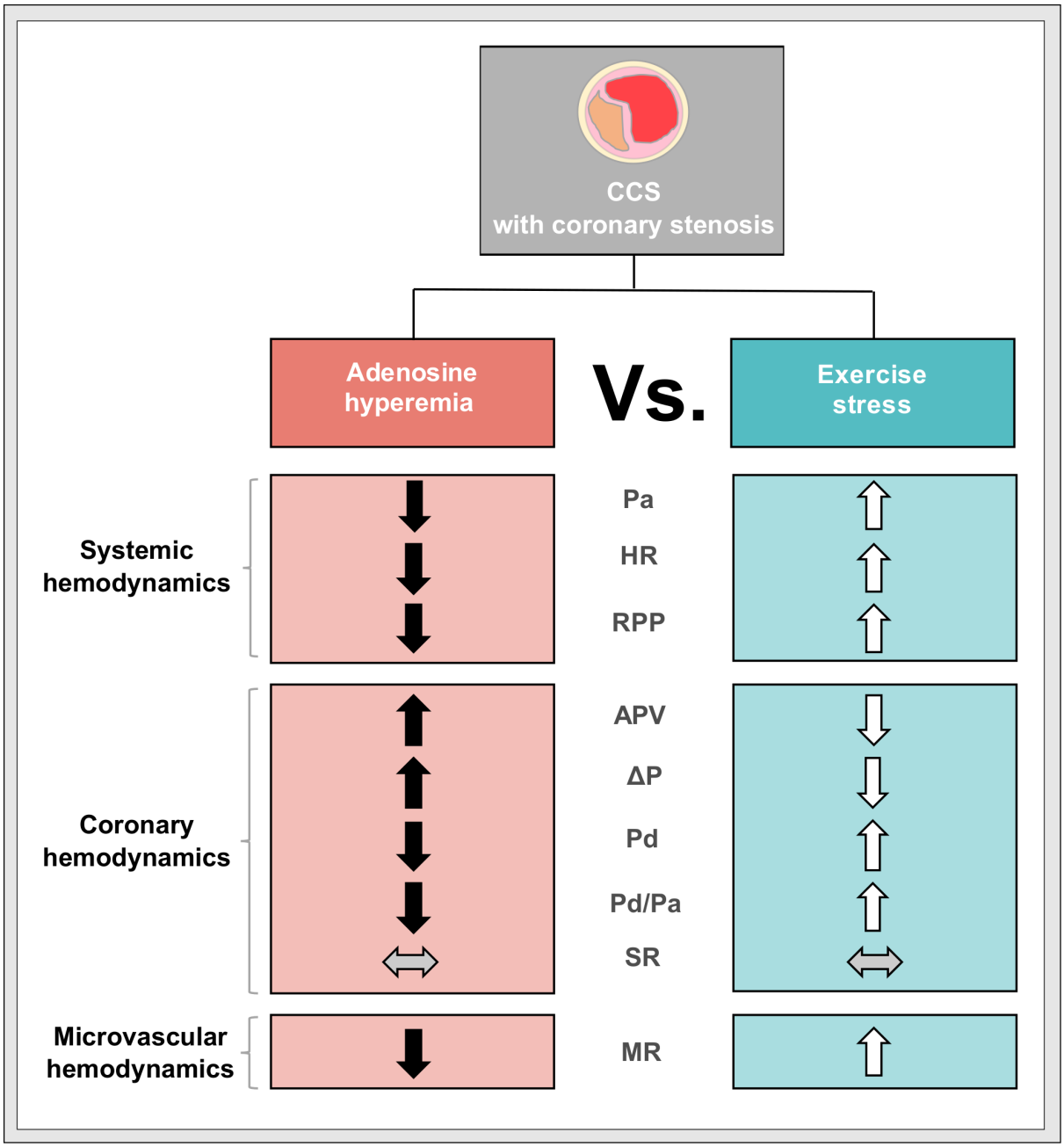

A)
Microvascular resistance
p=0.001
mmHg.cm−1.sec−1
7.5
5.0
2.5
Adenosine
Exercise
B)
Microvascular resistance
*
mmHg.cm−1.sec−1
5
4
3
0min
1min
Half max
Max

Figure 4.


CCS
with coronary stenosis
Adenosine hyperemia
Vs.
Exercise stress
Systemic hemodynamics
Pa
HR
RPP
Coronary hemodynamics
APV
ΔP
Pd
Pd/Pa
SR
Microvascular hemodynamics
MR