Effect of Physical Endurance Exercise Training on Coronary Artery Structure and Function in Healthy Men: an Invasive Follow-up Study

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Abstract

Background: The purpose of this study in healthy young male volunteers without cardiovascular disease or risk factors was to quantify the changes in coronary artery size and function in response to regular physical endurance exercise.

Methods: In 8 healthy male volunteers (cardiologists; age 36±5 years), bicycle spiroergometry, Doppler echocardiography, and quantitative coronary angiography with intracoronary Doppler measurements before and after completion of a physical endurance exercise program of >5 months duration were performed. Right and left coronary angiography was first done without medication. Flow-induced (hyperemic) endothelium-dependent left coronary artery vasodilatation was determined using intracoronary adenosine. Endothelium-independent vasodilatation of the left coronary artery was assessed using nitroglycerin. Coronary flow velocity reserve was determined by intracoronary Doppler measurement using adenosine.

Results: After the exercise program, maximum oxygen uptake increased from 46±6 to 54±5ml/min/kg (p=0.04), maximum ergometric workload changed from 3.8±0.3 to 4.4±0.3Watt/kg (p=0.001), and left ventricular mass index increased from 82±18 to 108±29g/m² (p=0.001). The right, left main and left anterior descending coronary artery cross-sectional area increased significantly in response to exercise. Before versus at the end of the exercise program, flow-induced left anterior descending coronary artery cross-sectional area was 10.1±3.5mm² and 11.0±3.9mm², respectively (p=0.03), nitroglycerin-induced left coronary calibres increased significantly, and coronary flow velocity reserve changed from 3.8±0.8 to 4.5±0.7 (p=0.001). Left coronary artery calibre correlated significantly with ventricular mass and maximum oxygen uptake, and coronary flow velocity reserve was significantly associated with maximum workload.

Conclusions: Regular physical endurance exercise in young men without cardiovascular disease or risk factors results in an adaptive increase of epicardial coronary artery size, in improved vasodilatation and in enhanced hyperemic microcirculatory reserve.

Condensed Abstract
In 8 healthy male volunteers (cardiologists; age 36±5 years), bicycle spiroergometry, Doppler echocardiography, and quantitative coronary angiography with intracoronary Doppler measurements before and after completion of a physical endurance exercise program of >5 months duration were performed. Maximum oxygen uptake increased from 46±6 to 54±5ml/min/kg (p=0.04), maximum ergometric workload changed from 3.8±0.3 to 4.4±0.3Watt/kg (p=0.001), and left ventricular mass index increased from 82±18 to 108±29g/m² (p=0.001). The right, left main and left anterior descending coronary artery cross-sectional area increased significantly in response to exercise. Before versus at the end of the exercise program, flow-induced left anterior descending coronary artery cross-sectional area was 10.1±3.5mm² and 11.0±3.9mm², respectively (p=0.03), nitroglycerin-induced left coronary calibres increased significantly, and coronary flow velocity reserve changed from 3.8±0.8 to 4.5±0.7 (p=0.001). Left coronary artery correlated significantly with ventricular mass and maximum oxygen uptake, and coronary flow velocity reserve was significantly associated with maximum workload.

Key Words
Coronary circulation, endothelial function, exercise.
Introduction

Cardiovascular diseases, in particular coronary artery disease (CAD), represent the leading cause (>40%) of death in industrialized countries [1]. Meta-analyses of the effects of exercise training on morbidity and mortality in patients after myocardial infarction concluded that regular physical exertion favorably influenced mortality but not reinfarction [2]. Possibly even more important, increased occupational or recreational physical activity reduces the risk of cardiac death in individuals who have not yet shown manifestations of CAD, i.e. primary prevention [3]. Hence, physical exercise is recommended for both primary [4] and secondary [5] prevention of cardiovascular disease.

Despite the epidemiologic data strongly supporting the existence of a relation between exercise and reduced risk of CAD, clinical evidence for the mechanisms responsible for this association has been provided only very recently and exclusively in the case of secondary prevention [6]. Aside from the favorable effect of exercise on the severity of cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia or obesity [5], exercise appears to be cardioprotective independently of the traditional risk factors [7]. Hambrecht et al. provided evidence for a link between endothelial function and exercise training in patients with CAD by directly documenting that a 4-week exercise training improved endothelium-dependent vasodilatation both in coronary epicardial and resistance vessels [6]. A thorough longitudinal investigation in humans on the mechanisms related to the primary preventive effect of endurance exercise on CAD is lacking so far. The only available preliminary data pertain to a cross-sectional comparison of coronary artery sizes between endurance athletes and hypertensive patients undergoing diagnostic coronary arteriography [8].

Therefore, the purpose of this study in healthy young volunteers without cardiovascular risk factors was to quantify the changes in coronary artery size and function (i.e.
endothelium-dependent and -independent coronary vasomotion and coronary flow reserve) in response to regular physical endurance exercise.

Methods

Study subjects
Eight healthy volunteers (male cardiologists; age 36±5 years) without cardiovascular risk factors (except for one occasional smoker) consented to participate in the study. Each individual served as his own control. All subjects underwent plasma lipid level assessment, bicycle spiroergometry, Doppler echocardiography, and coronary angiography with intracoronary Doppler guidewire measurements before and after completion of a physical endurance exercise program of at least 5 months.

Endurance exercise program
The exercise program consisted of running or cycling at least 4 times per week for a duration of at least 60 minutes per session over a minimal time period of 5 months. Target heart rate during the sessions was required to be 80% of the heart rate at peak oxygen uptake (VO$_2$max, ml/min/kg body weight) determined during spiroergometry before the exercise program. Survey of the exercise program was performed by digital pulse recording and by repeat spiroergometry at the end of the exercise program (termed "after exercise").

Bicycle spiroergometry
Before each spiroergometry, the weight of the subject was determined. A venous blood sample was taken for the determination of plasma lipid levels. Bicycle spiroergometry was performed until exhaustion using a protocol with workloads starting at 125 Watt and increasing every 3 minutes by 25 Watt. During ergometry, VO$_2$max was continuously measured via a face mask, heart rate was recorded constantly, and sphygmomanometric blood pressure was obtained every 3 minutes. Maximum
workload was defined as the peak workload sustained over the entire 3 minutes of a particular workload level.

**Doppler echocardiography**

Doppler echocardiographic exams were performed within one day before or after spiroergometry and coronary angiography using an Acuson Sequoia C256 (Acuson Inc., Mountainview, CA, USA) with a 4-MHz transducer with second harmonic imaging and Doppler tissue imaging (DTI) technology. Subjects were in supine, left-lateral position, and underwent conventional M-mode and 2-dimensional echocardiography from a left parasternal and apical window. M-mode measurements of the left ventricle were obtained in triplicate at end-diastole and end-systole according to the recommendations of the American Society of Echocardiography [9]. They included septal and posterior wall thickness, left ventricular and left atrial cavity dimensions according to the leading edge method. Left ventricular mass was determined according to the cube formula using end-diastolic values of septal and posterior wall thickness and left ventricular cavity dimension [10]. Left ventricular volume measurements for the calculation of left ventricular ejection fraction were performed in biplane projection from apical two- and four-chamber views [11]. Left ventricular volumes were computed using the biapical Simpson rule.

The purpose of assessing left ventricular diastolic function was to exclude the development of impaired ventricular relaxation during exercise-induced increase of left ventricular mass. Left ventricular diastolic function was assessed from the apical four-chamber view using transmitral Doppler flow velocity, and mitral annular motion velocity measurements [12]. The pulsed-wave sample volume of the conventional Doppler was placed at the tips of the mitral leaflets. The obtained variables included peak flow velocity (E, m/sec) and deceleration time (msec) of early diastolic transmitral filling, peak flow velocity (A, m/sec) of late diastolic transmitral filling, and isovolumetric relaxation time (msec). Mitral annular motion velocity during early diastole (cm/sec) was
performed using Doppler tissue imaging with the pulsed-wave sample volume placed at the septal, lateral, inferior and anterior mitral annulus from the apical four- and two-chamber view, respectively. The respective values obtained at these locations were averaged. Early diastolic mitral annular motion velocities =8cm/sec have been documented to accurately detect impaired left ventricular relaxation independent of cardiac loading conditions [12].

Quantitative coronary angiography
All subjects underwent biplane coronary angiography from the right femoral artery approach using 5F right and left Judkins coronary catheters. Care was taken to use identical right (RAO) and left anterior oblique (LAO) projections as well as X-ray focal-spot-to-image-intensifier distances during the baseline and the follow-up exams. Digitized end-diastolic frames were analyzed by an automatic contour edge detection algorithm [13]. Coronary artery calibres were measured quantitatively using the coronary catheter for calibration. Measurements were performed over a distance of 4-8mm in triplicate and averaged at each location. End-diastolic coronary artery diameters were obtained at the left main, the proximal, mid and distal segment of the right, the proximal and mid segment of the left anterior descending, and the proximal and mid segment of the left circumflex coronary artery. Coronary artery cross-sectional area was calculated as both half diameters times π (ellipse formula). Two coronary side branch landmarks were used to reproduce identical measurement sites during both exams. The latter were chosen midway between the sidebranches.

Coronary Doppler flow velocity measurements
As coronary microvascular function parameter, adenosine-induced (see below) coronary flow velocity reserve (CFVR) was determined with a 0.014" Doppler angioplasty guidewire featuring a 12-MHz piezoelectric crystal at its tip (Flowire®, Endosonics, Mountain View, CA, USA) placed in the mid LAD and LCX. The Doppler guidewire has been validated to measure phasic flow velocity patterns accurately and to
track changes in flow rate linearly [14]. CFVR was determined by dividing maximum hyperemic peak flow velocity (induced by 18µg intracoronary adenosine bolus [15]) averaged over three cardiac cycles by average peak flow velocity during resting conditions. During CFVR measurements (in triplicate), the epicardial coronary artery calibre was maintained constant by pretreatment with 200µg of intracoronary nitroglycerin.

Study protocol of the invasive exams
Before coronary angiography, 5000 units of intravenous heparin were given. Biplane coronary angiography of the right and the left coronary artery was performed without any vasoactive drugs. Subsequently, an interval of 10 minutes was allowed for dissipation of the vasomotor effect of the nonionic contrast medium (ioversol 300). Left coronary angiography was repeated immediately after injection of a bolus of 18µg of adenosine via the left coronary Judkins catheter. Again, a 10-minutes interval was allowed following coronary angiography with adenosine. Subsequently, an intracoronary bolus of 200µg of nitroglycerin was given. Biplane left coronary angiography was repeated immediately afterwards. The Doppler guidewire was then placed in the mid LAD via the diagnostic 5F Judkins catheter. CFVR was determined by flow velocity measurements during resting conditions and during hyperemia after intracoronary bolus injection of 18µg adenosine. CFVR measurements were performed in triplicate and averaged. The Doppler guidewire was then placed in the mid LCX, and CFVR measurements were performed identically (i.e. a total of 6 measurements per subject and exam). Coronary flow velocity was monitored continuously on video tape during the entire procedure of Doppler measurements.

Statistical analysis
Intraindividual comparisons between the exams before and after the exercise program of continuous allometric, hemodynamic, spiroergometric, echocardiographic and invasive data were performed by a paired Student's t-test. Curvilinear (i.e. power equation fitting) and linear regression analysis was used for assessing the relation between left main coronary artery calibre and CFVR, and left ventricular mass, exercise endurance and maximum workload, respectively. Linear regression analysis with calculation of the standard error of estimate (SEE) was used to determine the variability between repetitive measurements at baseline and follow-up. Mean values ± standard deviation are given. Statistical significance was defined at a p value of <0.05.

Results

Subject characteristics
All individuals finished the exercise program and underwent complete follow-up exams after a duration of 9±5 months. None of the subjects was under treatment with medicaments. Body weight and surface area decreased significantly during the exercise period (table 1). Resting heart rate and systemic blood pressure obtained immediately before Doppler echocardiography did not change during the exercise period. Plasma total cholesterol levels tended to decrease, while HDL and LDL cholesterol as well as triglyceride levels remained constant (table 1).

Bicycle spiroergometry
There were no statistically significant differences in minimal or maximally achieved heart rate or systemic blood pressure during ergometry within the individuals before versus after the exercise program (table 2). Maximum VO₂ normalized for body weight, maximum ergometric workload and maximum workload per body weight increased significantly during the exercise period (table 2).

Doppler echocardiography
End-diastolic interventricular septal and posterior wall thickness of the left ventricle and left ventricular mass as well as mass index increased significantly during the exercise program (table 3). The standard error of estimate (SEE) between the two of three measurements of left ventricular mass index farthest apart was 15g/m² at baseline and 12g/m² at follow-up (18% and 11% of the respective mean value). End-diastolic and end-systolic left ventricular and left atrial diameter, respectively as well as ejection fraction were not altered significantly. Despite the ventricular hypertrophic response occurring in all study individuals (one of them reaching the definition for left ventricular hypertrophy, i.e. >134g per m² of body surface area), all transmitral and mitral annular Doppler parameters for diastolic function remained normal and statistically unchanged during the exercise program (table 3).

Coronary artery structural and functional data

All of the individuals had a right dominant coronary artery circulation. The standard error of estimate (SEE) between the two of three measurements of coronary artery diameter farthest apart was 0.02mm at baseline and 0.01mm at follow-up (0.7% and 0.3% of the respective mean value). In the absence of any vasoactive drug, coronary artery cross-sectional areas at all except two measurement sites (distal RCA and LCX) increased significantly in response to the exercise program (table 4 and figure 1). The combined left main plus proximal RCA cross-sectional areas normalized for 100g of left ventricular myocardial mass was 17.5±6.1mm² before and 16.7±5.5mm² after the exercise program (p=not significant).

In response to intracoronary adenosine (i.e. flow-dependent or hyperemic vasodilatation), the proximal left coronary artery calibres increased significantly following the exercise program, whereas the mid LAD and LCX segements did not (table 4).
Endothelium-independent vasodilatation using nitroglycerin showed significantly larger coronary artery calibres after compared to before exercise at the site of the left main coronary artery, and at the mid LAD and proximal LCX segment (table 4). Left main coronary artery vasodilatation in response to nitroglycerin was +10.1±4.6% before and ±18.9±7.5% after the exercise program (p=0.02). There was a power-law relation between all left ventricular mass values (i.e. those before and after the exercise program) and the corresponding nitroglycerin-induced left main coronary artery calibres, whereby all except one individual showed an enlarged vessel calibre following endurance exercise (figure 2). There was a direct association between all values of maximum normalized VO$_2$ and the corresponding nitroglycerin-induced left main coronary artery calibres (figure 3).

Adenosine-induced left coronary artery flow velocity reserve (i.e. LAD and LCX) increased significantly in response to the exercise program (table 4 and figure 4). The standard error of estimate (SEE) between the two of three measurements of coronary flow velocity reserve farthest apart was 0.31 at baseline and 0.1 at follow-up (7.6% and 2.4% of the respective mean value). There was a direct correlation between all maximum normalized ergometric workload values and the corresponding coronary flow velocity reserve (figure 5).

Discussion

This study in healthy young male volunteers without cardiovascular disease or risk factors documents for the first time that epicardial coronary artery size and vasodilatation increase, and that the capacity to augment coronary flow during hyperemia improves in response to a sustained endurance exercise program. These changes go hand in hand with a physiologic hypertrophic response of the left ventricle and with improved endurance and maximum workload capacity.
Exercise-induced alterations of vascular structure and associated changes

In this context, the questions may be raised whether an increase in size is a structural vascular remodeling or whether it is a chronic vasodilatation, and, more importantly, whether regarding coronary artery size "bigger is really better" [16].

Control of vascular diameter by instantaneous flow alterations is an acute phenomenon which was first described by Schretzenmayr [17]. It obviously precedes structural changes in response to chronic blood flow alterations [18]. Our endurance exercise program was associated with bigger coronary arteries at 28 of a total of 32 proximal coronary angiographic measurement sites (figure 1). The finding of enlarged nitroglycerin induced arterial calibre following the exercise program indicates structural adaptation of the coronary arteries. Data from various animal models indicate that vigorous endurance exercise training enlarges the diameter of coronary arteries [19,20], and that increases in the canine carotid artery blood flow leading to a bigger vessel is related to an increased rate of protein turnover [21]. In the precise sense of "structural alterations", only the latter investigation provides evidence that actual arterial remodeling occurs as adaptive response to increased flow. Flow-mediated vasodilatation (i.e. function, see below) is vascular endothelium-dependent, and so is flow-mediated vascular remodeling. Langille and O'Donnell [22] found that a long-term decrease in flow through the rat carotid artery causes the vessel to "shrink", a response which is abolished by removal of the endothelium. One possible concept underlying this flow-adapted remodeling of vascular structure is that of the maintenance of flow-related shear forces within certain limits, a basic principle which has been documented to apply also to the human coronary artery tree [13].

So far, no information has been available from longitudinal secondary or primary prevention studies about the effect of exercise training on absolute coronary artery calibre. Hambrecht and coworkers did not provide absolute coronary artery calibre data
of their patients with coronary artery disease undergoing a 4-week intensive exercise program [6]. Considering the abovementioned experimental investigations, it can be speculated that the duration of their exercise program was too short to produce vascular calibre increase at rest. Surprisingly, Haskell et al. [8] found in their cross-sectional angiographic study no statistical difference in coronary artery calibres between ultradistance runners and inactive men without coronary artery stenoses. While running more than 4000km per year in these normotensive athletes had led to concentric left ventricular hypertrophy, systemic arterial hypertension led also to increased left ventricular mass among control patients. This may explain the similar coronary artery calibres in the two groups. In order to account for the fact that exercise-induced hypertrophic response was physiologic in our study and not pathologic with disturbed ventricular relaxation as it occurs in hypertensive heart disease, diastolic left ventricular function was assessed and found to remain normal following exercise training.

Several lines of evidence in our study support the concept suggested above of an association between coronary artery calibre and left ventricular mass. Whereas the largest exercise-related increases in coronary artery calibre among our study individuals with exclusively right dominant coronary arteries occurred in the left main and proximal right coronary artery, no calibre changes were observed in the small left circumflex coronary arteries. All but one individual showed concordant increases in coronary artery calibre and left ventricular mass, and the observed relation between vessel calibre and ventricular mass (figure 2) was close to the 2/3-power relation theoretically predicted by the law of minimum viscous energy loss in the transport of blood [13]. Aside from variations in left ventricular mass, variable levels of endurance (i.e. VO2max, figure 3) were related to coronary artery calibres in our study, whereby both together accounted for less than half of the statistical variability in vessel calibres.

With respect to the initially raised question whether bigger coronary artery calibres are better, the considerations outlined favor the notion that larger calibres irrespective of
functional characteristics represent just an adaptive response to increased left ventricular mass and to enhanced myocardial oxygen consumption with augmented flow. Conversely, improved endothelium-dependent function of the coronary arteries seems to actually confer an outcome benefit as recent data have indicated [23].

**Exercise-induced changes in coronary artery function and associated alterations**

Endothelial vasodilator dysfunction has been observed in patients with cardiovascular risk factors, even in the absence of overt atherosclerotic lesions [24,25]. Endothelial function has been hypothesized to serve as an indicator reflecting the overall stress imposed by coronary risk factors [26]. So far, it has been unknown whether in entirely healthy young men correction of sedentary lifestyle is associated with improved coronary vasomotion. Two aspects of coronary vasomotor function were tested in our study, namely flow-mediated (i.e. mostly nitric oxide mediated) epicardial vasodilatation and microvascular function. Both, flow-induced epicardial vasodilatation and coronary flow reserve improved in response to the exercise program. Since vasodilatation in response to increased flow is mediated by release of nitric oxide [27,28], flow-induced vasodilatation as it occurred at proximal sites of the left coronary artery in our study is regarded as endothelium-dependent. However, biosynthesis or bioavailability of nitric oxide was not directly measured in our study. Thus, the term “endothelium-dependent” cannot be used strictly; the greater flow-mediated vasodilation after the exercise program might have resulted from an enhanced vascular smooth muscle sensitivity to nitric oxide without altered availability of the latter. To keep the invasive study protocol simple in our individuals without cardiovascular disease or risk, standard testing of endothelium-dependent coronary vasomotor function by acetylcholine [29], a substance which causes direct release of nitric oxide, was not performed. The clinical relevance of endothelial vasodilator dysfunction among patients at risk of coronary atherosclerosis has been recently demonstrated by showing that it is predictive of future cardiovascular events irrespective of a specific mechanism (i.e. acetylcholine-, flow- or sympathetically
mediated) to mediate endothelium-dependent vasodilatation [23]. A beneficial primary preventive effect of improved endothelium-dependent vasodilatation in response to exercise cannot be directly extrapolated from our on the basis of the mentioned study, but the mechanism mediating the effect seems to be identical.

Endothelium-independent vasodilatation using nitroglycerin was improved in our trained individuals in keeping with the study of Haskell et al. [8]. However, the improved nitroglycerin-induced dilatation of coronary arteries of trained athletes in the study by Haskell et al. was not documented in comparison with an untrained baseline status in the same individuals, but rather versus a sedentary hypertensive control population with pathologic left ventricular hypertrophy [8]. The 4-week endurance training period employed in the study by Hambrecht et al. [6] among patients with coronary artery disease revealing no beneficial effect on endothelium-independent vasomotion indicates that high-intensity training over a longer period may be necessary to increase the capacity of coronary vessels for endothelium-independent dilatation.

Improved vasodilating capacity of the microcirculation in response to exercise training has been documented experimentally [30], and, very recently, in patients with coronary artery disease [6], but not in the setting of primary cardiovascular prevention. Adenosine-induced coronary flow reserve before the exercise program was markedly lower than the values around 4.5 in the left coronary artery described by Wilson et al. [15]. This is surprising, since patients with chest pain and not entirely healthy, and fairly well trained persons to start with underwent diagnostic coronary angiography in that study. The finding that it is the maximally achievable workload (normalized for body weight) which is directly associated with the maximally attainable coronary blood flow is original, and it makes sense intuitively. Furthermore, our data are physiologically plausible in that the coronary flow reserve achieved in the absence of any physical work does not fall below 1, a value indicating coronary steal which does not occur in a normal coronary circulation [31].
Study limitations
Aside from the limitations alluded to above, the low number of study individuals included is of relevance. This is reflected in increased coronary artery calibres following exercise which at some measurement sites did not reach statistical significance, a fact which most likely could have been corrected by investigating more subjects. The pool of healthy, young men interested in engaging in a long-term exercise program and willing to undergo two coronary angiograms with intracoronary measurements is limited particularly because only cardiologists were eligible as they had to be fully cognizant of the potential risks of the study.

In conclusion, regular physical endurance exercise in young men without cardiovascular disease or risk factors results in an adaptive increase of epicardial coronary artery calibres, in improved vasodilatation and in enhanced hyperemic microcirculatory reserve.

References


**Figures**

**Figure 1** Individual changes of coronary artery cross-sectional area before (before exercise) and at the end (after exercise) of the endurance exercise program. The circular symbols with error bars denote mean values ± standard deviation. NS=not significant.

**Figure 2** Correlation between left ventricular mass before (open symbols) and at the end (closed symbols) of the exercise program, and nitroglycerin (NTG)-induced left main coronary artery cross-sectional area (vertical axis). The bold line indicates the significant curvilinear regression between the two parameters. The thin lines connect individual ventricular mass- / coronary calibre-values before and after the exercise program.

**Figure 3** Correlation between maximum oxygen consumption (VO\(_2\)max) normalized for body weight (horizontal axis) before (open symbols) and at the end (closed symbols) of the exercise program, and nitroglycerin (NTG)-induced left main coronary artery cross-sectional area (vertical axis). The bold line indicates the
significant direct regression between the two parameters. The thin lines connect individual VO\textsubscript{2}max per body weight / coronary calibre-values before and after the exercise program.

**Figure 4** Individual changes of adenosine-induced coronary flow velocity reserve before (before exercise) and at the end (after exercise) of the endurance exercise program. The circular symbols with error bars indicate mean values ± standard deviation.

**Figure 5** Correlation between maximum normalized ergometric workload (horizontal axis) before (open symbols) and at the end (closed symbols) of the exercise program, and coronary flow velocity reserve (vertical axis). The thin line indicates the significant direct regression between the two parameters.
### Table 1

**Subject characteristics and clinical data**

<table>
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<th></th>
<th>Before exercise program</th>
<th>After exercise program</th>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36±5</td>
<td>37±5</td>
<td></td>
</tr>
<tr>
<td>Duration of training period (months)</td>
<td>9±5</td>
<td>9±5</td>
<td></td>
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<tr>
<td>Height (cm)</td>
<td>180±7</td>
<td>180±7</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72±7</td>
<td>68±6</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.91±0.12</td>
<td>1.86±0.11</td>
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<td>Heart rate at rest (beats per minute)</td>
<td>63±13</td>
<td>63±15</td>
<td>NS</td>
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<tr>
<td>Systolic blood pressure at rest (mmHg)</td>
<td>116±21</td>
<td>129±2</td>
<td>NS</td>
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<tr>
<td>Diastolic blood pressure at rest (mmHg)</td>
<td>67±14</td>
<td>74±7</td>
<td>NS</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.5±0.3</td>
<td>4.3±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.6±0.2</td>
<td>1.4±0.2</td>
<td>NS</td>
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<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.5±0.4</td>
<td>2.5±0.4</td>
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<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.7±0.3</td>
<td>0.8±0.2</td>
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</table>

Abbreviations: HDL=high density lipoprotein; LDL=low density lipoprotein; NS=not significant.
### Table 2

<table>
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<th>Before exercise program</th>
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<tr>
<td><strong>Heart rate and systemic blood pressure</strong></td>
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<tr>
<td>Peak heart rate (beats per minute)</td>
<td>175±15</td>
<td>178±8</td>
<td>NS</td>
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<tr>
<td>Peak systolic blood pressure (mmHg)</td>
<td>171±7</td>
<td>187±13</td>
<td>NS</td>
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<td><strong>Physical endurance (oxygen uptake)</strong></td>
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<td></td>
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</tr>
<tr>
<td>Maximum VO2 / kg body weight (ml/min/kg)</td>
<td>46±6</td>
<td>54±5</td>
<td>0.04</td>
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<td><strong>Physical workload</strong></td>
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<tr>
<td>Maximum workload (Watt)</td>
<td>271±28</td>
<td>300±35</td>
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<td>Maximum normalized workload (Watt/kg body weight)</td>
<td>3.8±0.3</td>
<td>4.4±0.3</td>
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</table>

Abbreviations: NS=not significant; VO2=oxygen uptake.
Table 3

<table>
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<th>Doppler echocardiography</th>
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<tr>
<td>Interventricular septal thickness (end-diastole mm)</td>
<td>9.4±1.7</td>
<td>11.2±0.2</td>
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<td>Posterior wall thickness (end-diastole, mm)</td>
<td>8.3±1.0</td>
<td>10.7±2.7</td>
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<td>End-diastolic left ventricular diameter (mm)</td>
<td>50.6±5.5</td>
<td>50.3±0.5</td>
<td>NS</td>
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<tr>
<td>End-systolic left ventricular diameter (mm)</td>
<td>30.0±4.0</td>
<td>33.0±4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>38.0±4.0</td>
<td>35.0±7.0</td>
<td>NS</td>
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<tr>
<td>Left ventricular mass (g)</td>
<td>158±40</td>
<td>203±63</td>
<td>0.003</td>
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<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>82±18</td>
<td>108±29</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>67±6</td>
<td>69±6</td>
<td>NS</td>
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</table>

**Left ventricular diastolic function**

| Early diastolic transmitral peak flow velocity (E; cm/sec) | 0.65±0.08 | 0.67±0.11 | NS    |
| Late diastolic transmitral peak flow velocity (A; cm/sec) | 0.39±0.11 | 0.44±0.07 | NS    |
| E / A ratio | 1.8±0.5 | 1.6±0.4 | NS    |
| E deceleration time (msec) | 167±22 | 180±67 | NS    |
| Isovolumetric relaxation time (msec) | 71±8 | 72±10 | NS    |
| Early diastolic mitral annular motion velocity (cm/sec) | 17.9±1.1 | 15.7±3.0 | NS    |

**Abbreviations:** NS=not significant.
Table 4

**Coronary artery structural and functional data**

<table>
<thead>
<tr>
<th></th>
<th>Before exercise program</th>
<th>After exercise program</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main + right coronary artery (mm²)</td>
<td>26.1±5.3</td>
<td>32.1±7.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Left main coronary artery (mm²)</td>
<td>16.1±3.4</td>
<td>17.1±3.6</td>
<td>0.0006</td>
</tr>
<tr>
<td>RCA: proximal (mm²)</td>
<td>10.1±3.3</td>
<td>15.1±4.7</td>
<td>0.03</td>
</tr>
<tr>
<td>RCA: mid segment (mm²)</td>
<td>8.4±2.9</td>
<td>9.4±2.9</td>
<td>0.03</td>
</tr>
<tr>
<td>RCA: distal (mm²)</td>
<td>5.2±1.9</td>
<td>5.7±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>LAD: proximal (mm²)</td>
<td>9.5±2.9</td>
<td>10.1±3.3</td>
<td>0.03</td>
</tr>
<tr>
<td>LAD: mid segment (mm²)</td>
<td>4.9±1.5</td>
<td>5.3±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LCX: proximal (mm²)</td>
<td>5.0±2.5</td>
<td>5.2±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Left main coronary artery: after ADO (mm²)</td>
<td>17.0±3.9</td>
<td>18.8±3.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LAD: proximal: after ADO (mm²)</td>
<td>10.1±3.5</td>
<td>11.0±3.9</td>
<td>0.03</td>
</tr>
<tr>
<td>LAD: mid segment: after ADO (mm²)</td>
<td>5.6±1.6</td>
<td>5.7±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>LCX: proximal: after ADO (mm²)</td>
<td>5.3±3.1</td>
<td>5.6±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Left main coronary artery: after NTG (mm²)</td>
<td>17.7±3.6</td>
<td>20.2±4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>LAD: proximal: after NTG (mm²)</td>
<td>11.0±4.1</td>
<td>12.2±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>LAD: mid segment: after NTG (mm²)</td>
<td>6.3±2.0</td>
<td>6.9±2.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LCX: proximal: after NTG (mm²)</td>
<td>6.1±3.1</td>
<td>6.6±3.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Coronary flow velocity reserve (n=16)</td>
<td>3.8±0.8</td>
<td>4.5±0.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Abbreviations: ADO=intracoronary adenosine 18µg; LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; NS=not significant; NTG=intracoronary nitroglycerine 200µg; RCA=right coronary artery.
Figure 1

Left main coronary artery

Right coronary artery (proximal)

Left anterior descending coronary artery (proximal)

Left circumflex coronary artery (proximal)

Windecker et al.
Figure 2

NTG-induced left main coronary artery cross-sectional area (mm²) vs. left ventricular mass (g).

- △ before exercise
- ▲ after exercise

Equation: \( y = 1.6 + x^{0.5} \)

\( r = 0.58, p = 0.03 \)
Figure 3

NTG-induced left main coronary artery cross-sectional area (mm²) vs. VO₂ max / kg body weight (ml/min/kg)

\[ x = 0.03 + 0.31y \]

\[ r = 0.24, p < 0.05 \]
Figure 4

Left anterior descending and left circumflex coronary flow velocity reserve

Coronary flow velocity reserve

before exercise  after exercise

p=0.001

Windecker et al.
Figure 5

The scatter plot shows the relationship between coronary flow velocity reserve (no unit) and maximum normalized workload (Watt/kg body weight) with data points indicating a positive correlation. The equation of the linear regression line is given as:

\[ y = 1.0 + 0.75x \]

with the following statistics:
- Sample size (n) = 32
- Correlation coefficient (r) = 0.37
- P-value (p) = 0.03

The symbols on the plot represent different conditions:
- Open squares: before exercise
- Solid squares: after exercise