$\dot{V}O_{2\text{peak}}$, Myocardial Hypertrophy, and Myocardial Blood Flow in Endurance-Trained Men

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ABSTRACT

LAAKSONEN, M. S., I. HEINONEN, M. LUOTOLAHTI, J. KNUUTI, and K. K. KALLIOKOSKI. $\dot{V}O_{2\text{peak}}$, Myocardial Hypertrophy, and Myocardial Blood Flow in Endurance-Trained Men. *Med. Sci. Sports Exerc.*, Vol. 46, No. 8, pp. 1498–1505, 2014. **Introduction:** Endurance training induces cardiovascular and metabolic adaptations, leading to enhanced endurance capacity and exercise performance. Previous human studies have shown contradictory results in functional myocardial vascular adaptations to exercise training, and we hypothesized that this may be related to different degrees of hypertrophy in the trained heart. **Methods:** We studied the interrelationships between peak aerobic power ($\dot{V}O_{2\text{peak}}$), myocardial blood flow (MBF) at rest and during adenosine-induced vasodilation, and parameters of myocardial hypertrophy in endurance-trained (ET, $n = 31$) and untrained ($n = 17$) subjects. MBF and myocardial hypertrophy were studied using positron emission tomography and echocardiography, respectively. **Results:** Both $\dot{V}O_{2\text{peak}}$ ($P < 0.001$) and left ventricular (LV) mass index ($P < 0.001$) were higher in the ET group. Basal MBF was similar between the groups. MBF during adenosine was significantly lower in the ET group (2.88 ± 1.01 vs 3.64 ± 1.11 mL·g⁻¹·min⁻¹, $P < 0.05$) but not when the difference in LV mass was taken into account. $\dot{V}O_{2\text{peak}}$ correlated negatively with adenosine-stimulated MBF, but when LV mass was taken into account as a partial correlate, this correlation disappeared. **Conclusions:** The present results show that increased LV mass in ET subjects explains the reduced hyperemic myocardial perfusion in this subject population and suggests that excessive LV hypertrophy has negative effect on cardiac blood flow capacity.

Key Words: HEART, PERFUSION, ENDURANCE TRAINING, POSITRON EMISSION TOMOGRAPHY

Chronic endurance training induces several morphological and functional cardiac adaptations, which have generally been considered physiological and beneficial for health and especially for fitness. One of the most prominent cardiac adaptations in a chronically trained heart is the increase in heart size, especially the left ventricular (LV) hypertrophy caused by wall thickening and cavity enlargement (44), the so-called *athlete's heart* (31).

Exercise training also causes changes in vascular function. Although studies in different patient groups with impaired vascular function show that endurance-type exercise training has the potential to improve peripheral and cardiovascular function, healthy endurance-trained (ET) subjects

seem not to have supranormal vascular function. For example, some studies have demonstrated reduced flow-mediated dilation in an athlete's peripheral artery (10) despite systemic remodeling (35). This apparent "athlete paradox", documented largely in peripheral arteries in humans to date, is explained by vascular remodeling that follows from repetitive short-term changes in arterial blood flow due to exercise training sessions (10,24). Cross-sectional studies in humans also generally suggest that cardiovascular function is normal in endurance athletes. Studies using positron emission tomography (PET) and [¹⁵O]H₂O to measure myocardial perfusion capacity show large variation in the results from reduced (13) to unchanged (17,18,32) and even increased (43) myocardial blood flow (MBF) during dipyridamole- or adenosine-induced vasodilation in ET subjects.

In addition to human studies, experiments performed in animals also show highly discrepant findings regarding exercise training and coronary blood flow capacity, as recently extensively reviewed by Laughlin et al. (24). Differences in results are likely to be explained by several factors such as differences in species, age, and sex, as well as duration, intensity, and type of exercise training. Interestingly, however, in animal studies that have reported increased cardiac blood flow capacity and in those where the used animal model

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most closely resembles the human heart, exercise training did not cause cardiac hypertrophy in dogs (23,26). In swine, higher LV-to-body mass ratio was documented (25,45), but this was due to the lower body weights and not absolutely higher LV mass. Although even fairly long-term (6 months) exercise interventions in previously untrained (UT) humans do not increase LV mass substantially (40), high LV mass is, however, one of the paramount features of highly trained endurance athletes (31). Importantly, in those swine studies where strenuous and long-term training produced substantial cardiac hypertrophy, cardiac capillary density was found to be reduced (3,46).

Along these lines, we hypothesized that large variation in previous human studies in relation to endurance training and myocardial vascular function might be related to the extent of LV hypertrophy. Accordingly, we investigated the interrelationships between peak aerobic power ($\dot{V}O_{2\text{peak}}$), MBF, and parameters of myocardial hypertrophy in ET and UT men. It was hypothesized on the basis of the animal studies that, because relative capillary density might be decreased in ET men with substantial cardiac hypertrophy, myocardial perfusion would also be reduced along the increments in LV hypertrophy.

METHODS

Subjects. Thirty-one healthy ET and 17 healthy UT men participated in the study (Tables 1 and 2). The subjects had no clinical or laboratory evidence of CHD, diabetes, or systemic hypertension, all were nonsmokers, and none of them were currently taking any medication. They also reported to have never experienced any unusual sensations even at maximal exercise, such as chest pain. ET subjects had a history of at least 4 yr (4–25 yr) of aerobic training (running, skiing, cycling, and orienteering) for at least three

TABLE 2. Hemodynamic parameters during the MBF measurements at basal state and during adenosine-induced vasodilation in ET ($n = 31$) and UT ($n = 17$) groups.

	ET	UT	P
Basal			
Systolic blood pressure (mm Hg)	121 $\pm$ 10	115 $\pm$ 9	0.04
Diastolic blood pressure (mm Hg)	67 $\pm$ 9	65 $\pm$ 9	0.40
MAP (mm Hg)	85 $\pm$ 8	82 $\pm$ 8	0.15
HR (bpm)	48 $\pm$ 8	59 $\pm$ 7	<0.001
Adenosine			
Systolic blood pressure (mm Hg)	124 $\pm$ 10	113 $\pm$ 10	0.001
Diastolic blood pressure (mm Hg)	68 $\pm$ 8	61 $\pm$ 11	0.03
MAP (mm Hg)	86 $\pm$ 7	79 $\pm$ 10	0.004
HR (bpm)	68 $\pm$ 15*	103 $\pm$ 11*	<0.001

* $P < 0.001$ versus basal value in the same group.

times per week (3–14 times per week). A written informed consent was obtained after the purpose, nature, and potential risks were explained to the subjects. The study was performed according to the Declaration of Helsinki, and the ethical committee of the Hospital District of Southwest Finland approved the study protocol.

Study design. Within 2 wk before the PET experiments, the $\dot{V}O_{2\text{peak}}$ was determined during an incremental cycling exercise test. PET studies were performed at least 2 h after a light breakfast, and subjects were instructed to avoid caffeinated beverages and exhaustive physical training during the last 24 h before the study. Before PET scanning, an echocardiography study was performed. Thereafter, a catheter was inserted in an antecubital vein for injection of [^{15}O]H₂O and the subjects were positioned in supine position into the PET scanner. MBF was then measured using [^{15}O]H₂O and PET at rest and during adenosine-induced vasodilation.

Determination of $\dot{V}O_{2\text{peak}}$. A standardized incremental bicycle test was performed until volitional exhaustion after a 10-min warm-up. $\dot{V}O_2$ was measured using the Medikro 202 gas analyzer (Medikro Oy, Kuopio, Finland) or MedGraphics cardiorespiratory diagnostic system (Medical Graphics Corp., St. Paul, MN) with 10-s sampling frequency. The mean of the three highest consecutive $\dot{V}O_2$ values within a 30-s time frame were considered as $\dot{V}O_{2\text{peak}}$.

PET measurements. Positron-emitting tracer ([^{15}O]H₂O) was produced as previously described (38). An ECAT 931/08 tomograph (Siemens/CTI Corp., Knoxville, TN), ECAT EXACT HR+ PET scanner (Siemens/CTI Corp., Knoxville, TN), and GE Advance PET scanner (General Electric Medical System, Milwaukee, WI) were used for image acquisition. Before the emission scan, a transmission scan for the correction of photon attenuation was performed. At baseline MBF measurements, [^{15}O]H₂O was injected intravenously for 2 min and dynamic PET scanning was started. After radioactivity decay (15 min), a similar MBF study was repeated during 6 min of intravenous administration of adenosine (140 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), which has been shown to induce maximal myocardial hyperemia (5). All PET data were corrected for dead time, decay, and measured photon attenuation, and PET images were processed using iterative reconstruction algorithms.

PET data analysis. Regions of interest were drawn on four representative and consecutive transaxial ventricular

TABLE 1. Characteristics of the study subjects in the ET ($n = 31$) and UT ($n = 17$) groups.

	ET	UT	P
Age (yr)	30 $\pm$ 8	25 $\pm$ 4	0.04
Height (cm)	182 $\pm$ 6	179 $\pm$ 6	0.11
Body mass (kg)	74 $\pm$ 7	76 $\pm$ 8	0.47
BMI ($\text{kg}\cdot\text{m}^{-2}$)	22 $\pm$ 2	24 $\pm$ 3	0.04
BSA (m^2)	1.95 $\pm$ 0.11	1.95 $\pm$ 0.11	0.87
$\dot{V}O_{2\text{peak}}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	60 $\pm$ 5	46 $\pm$ 5	<0.001
Longitudinal LVD (diastolic) (mm)	102 $\pm$ 6	96 $\pm$ 4	<0.001
Longitudinal LVD (systolic) (mm)	87 $\pm$ 5	81 $\pm$ 5	<0.001
Transverse LVD (diastolic) (mm)	56 $\pm$ 3	53 $\pm$ 3	<0.001
Transverse LVD (systolic) (mm)	35 $\pm$ 3	34 $\pm$ 3	0.15
Ejection fraction (%)	67 $\pm$ 4	66 $\pm$ 3	0.40
SV (mL)	105 $\pm$ 11	92 $\pm$ 9	<0.001
Resting cardiac output (L)	5.5 $\pm$ 0.9	5.5 $\pm$ 0.8	0.84
Septum thickness (diastolic) (mm)	11 $\pm$ 1	9 $\pm$ 1	<0.001
Septum thickness (systolic) (mm)	16 $\pm$ 2	14 $\pm$ 1	<0.001
Posterior wall thickness (diastolic) (mm)	11 $\pm$ 1	9 $\pm$ 1	<0.001
Posterior wall thickness (systolic) (mm)	17 $\pm$ 2	15 $\pm$ 1	<0.001
RWT	0.41 $\pm$ 0.04	0.33 $\pm$ 0.04	<0.001
LV mass (g)	330 $\pm$ 59	212 $\pm$ 33	<0.001
LV mass index ($\text{g}\cdot\text{m}^{-2}$)	169 $\pm$ 27	108 $\pm$ 13	<0.001
LV mass/height ^{2.7}	65 $\pm$ 11	44 $\pm$ 6	<0.001
LV work ($\text{mm Hg}\cdot\text{L}\cdot\text{min}^{-1}$)	433 $\pm$ 94	438 $\pm$ 73	0.84
LV work index ($\text{mm Hg}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$)	1.34 $\pm$ 0.34	2.10 $\pm$ 0.36	<0.001

BSA, body surface area; LVD, LV diameter.

slices covering the anterior and lateral free walls of the left ventricle. The regions of interest were drawn on the images obtained at rest and copied to the images obtained during maximal vasodilation. The input function was obtained from the LV time-activity curve, and thereafter, MBF was calculated using the previously introduced method using the single-compartment model (15). The mean MBF values of all the four planes at baseline and during hyperemia were calculated. Because LV work is known to be a good non-invasive indicator of myocardial $\dot{V}O_2$ demand, basal MBF was also normalized with LV work index using the following equation: basal MBF_{normalized} = measured basal MBF $\times$ (mean LV work index of the all subjects/individual LV work). Respectively, because blood flow is largely detached from metabolic control during pharmacologically induced hyperemia, hyperemic MBF values were individually normalized to correspond to the same perfusion pressure using the mean arterial pressure (MAP) and the following equation: hyperemic MBF_{normalized} = measured hyperemic MBF $\times$ (mean MAP of the all subjects/individual MAP). Coronary vascular resistance was calculated by dividing the mean arterial blood pressure by the respective MBF value. MBF reserve was defined as the ratio between hyperemic and baseline MBF. Both the absolute and the LV work- and MAP-normalized values were used in this regard.

Echocardiographic measurements and analyses.

Two-dimensional M-mode echocardiographic image acquisition was performed according to the recommendations of the American Society of Echocardiography. All echocardiographic recordings and analyses were performed by the same experienced investigator using a commercially available ultrasound scanner (Acuson Corp., Mountain View, CA). The study subjects rested for at least 15 min before their LV dimensions, and volumes were examined in a left lateral decubitus position. LV mass was calculated according to the Penn convention, as follows: LV mass = $1.04 \times [(\text{end-diastolic diameter} + \text{posterior wall thickness} + \text{septal thickness})^3 - \text{end-diastolic diameter}^3] - 13.6 \text{ g}$ (7). LV mass was indexed both into the body surface area (LV mass/body surface area) and height^{2.7} (LV mass/height^{2.7}) (2,8). LV work was calculated as stroke volume (SV) $\times$ HR $\times$ MAP, and it was also further normalized with LV mass (LV work index), as follows: (SV $\times$ HR $\times$ MAP)/LV mass. Relative wall thickness (RWT) was calculated as RWT = (posterior wall thickness + septal

thickness)/end-diastolic diameter. HR and blood pressure were automatically recorded with an ECG recorder (MAC 5000; GE Marquette Medical Systems, Milwaukee, WI) and with an automatic oscillometric blood pressure analyzer (Omrom, Tokyo, Japan), respectively, throughout the PET procedure.

Statistical analysis. Statistical analysis was performed using PASW Statistics 18 statistical software release 18.0.0 (SPSS Inc., Chicago, IL). The normal distribution of all parameters was first tested using the Kolmogorov-Smirnov non-parametric test. Student's *t*-test was used for the analysis of statistical difference between the trained and UT groups. In addition, ANCOVA with age or LV mass/height^{2.7} as controlled variable was used for group comparisons in blood flow parameters (Table 3). One-way ANOVA was used for comparison of differences in $\dot{V}O_{2\text{peak}}$ between the trained subgroups with different LV mass/height^{2.7} (ET₁ $\leq$ 60, *n* = 10; ET₂ = 60–70, *n* = 12; ET₃ > 70, *n* = 9). ANCOVA with age and body mass index (BMI) as covariates was used for the analysis of statistical differences between these trained subgroups and the UT group. Correlation values were calculated using Pearson correlation coefficient. Partial correlation was calculated with age or LV mass/height^{2.7} as controlled variable for all parameters reported in Table 4. A critical α level of 0.05 was adopted in all analyses. All data are shown as means $\pm$ SD.

RESULTS

Maximal aerobic power, echocardiographical findings, and hemodynamic parameters. ET subjects had 30% higher $\dot{V}O_{2\text{peak}}$ than UT subjects. Similarly, ET subjects had a significantly larger LV cavity and thicker myocardial walls compared with those of the UT subjects. LV mass and SV were also significantly increased in ET, whereas ejection fraction and cardiac output did not differ between the groups. In contrast, LV work index was lower in the ET.

Resting HR was lower but systolic blood pressure was higher in the ET group than those in the UT group during the determination of basal MBF. Adenosine infusion increased the HR in both groups but did not have any significant effect on blood pressure. Blood pressure remained higher and HR remained lower in the ET group than those in the UT group during hyperemia (Tables 1 and 2).

TABLE 3. Measured and normalized MBF, coronary resistance, and reserve in ET (*n* = 31) and UT (*n* = 17) subjects.

	ET	UT	<i>P</i> -unadj.	<i>P</i> -adj. 1	<i>P</i> -adj. 2
Basal MBF _{measured} (mL·g ⁻¹ ·min ⁻¹)	0.71 $\pm$ 0.19	0.73 $\pm$ 0.14	0.61	0.18	0.054
Basal MBF _{normalized} (mL·g ⁻¹ ·min ⁻¹)	0.87 $\pm$ 0.25	0.58 $\pm$ 0.14	<0.001	<0.001	0.003
Hyperemic MBF _{measured} (mL·g ⁻¹ ·min ⁻¹)	2.88 $\pm$ 1.01	3.64 $\pm$ 1.11	0.02	<0.001	0.38
Hyperemic MBF _{normalized} (mL·g ⁻¹ ·min ⁻¹)	2.78 $\pm$ 0.92	4.34 $\pm$ 1.65	0.001	<0.001	0.17
Perfusion reserve (basal MBF _{measured} /hyperemic MBF _{measured})	4.3 $\pm$ 1.6	5.0 $\pm$ 1.3	0.11	0.07	0.03
Perfusion reserve (basal MBF _{normalized} /hyperemic MBF _{normalized})	3.2 $\pm$ 1.2	6.5 $\pm$ 1.8	<0.001	<0.001	<0.001
Basal MBF in entire left ventricle (mL·min ⁻¹)	229 $\pm$ 62	154 $\pm$ 32	<0.001	<0.001	0.02
Hyperemic MBF in entire left ventricle (mL·min ⁻¹)	936 $\pm$ 328	762 $\pm$ 227	0.06	0.19	0.93
Basal coronary resistance (mm Hg·mL·g ⁻¹ ·min ⁻¹)	129 $\pm$ 34	115 $\pm$ 20	0.12	0.03	0.27
Hyperemic coronary resistance (mm Hg·mL·g ⁻¹ ·min ⁻¹)	35 $\pm$ 17	23 $\pm$ 7	0.01	<0.01	0.24

Basal MBF_{normalized}: basal MBF normalized with LV work index; hyperemic MBF_{normalized}: hyperemic MBF normalized with MAP; *P*-unadj., group comparison using *t*-test; *P*-adj. 1, group comparison using ANCOVA with age as a covariate; *P*-adj. 2, group comparison using ANCOVA with LV mass/height^{2.7} as a covariate.

TABLE 4. Correlations between $\dot{V}O_{2\text{peak}}$, basal and hyperemic MBF, and echocardiographic variables in ET, UT, and both groups combined (all).

	ET			UT			All		
	$\dot{V}O_{2\text{peak}}$	Basal MBF	Hyperemic MBF	$\dot{V}O_{2\text{peak}}$	Basal MBF	Hyperemic MBF	$\dot{V}O_{2\text{peak}}$	Basal MBF	Hyperemic MBF
$\dot{V}O_{2\text{peak}}$	—	—0.33 (0.74)	—0.39 (<0.05)	—	—0.51 (<0.05)	0.00 (0.99)	—	—0.27 (0.06)	—0.40 (<0.01)
SV	0.14 (0.47)	—0.38 (<0.05)	—0.34 (0.07)	—0.38 (0.13)	0.18 (0.50)	—0.14 (0.59)	0.43 (<0.01)	—0.24 (0.10)	—0.40 (<0.01)
TLVD (diastolic)	0.20 (0.28)	—0.36 (<0.05)	—0.37 (<0.05)	—0.35 (0.17)	0.22 (0.41)	—0.14 (0.61)	0.38 (<0.01)	—0.19 (0.18)	—0.39 (<0.01)
ST (diastolic)	0.08 (0.67)	—0.18 (0.33)	—0.06 (0.77)	—0.02 (0.95)	—0.39 (0.13)	—0.20 (0.45)	0.65 (<0.001)	—0.20 (0.17)	—0.32 (0.03)
PWT (diastolic)	0.09 (0.63)	—0.20 (0.28)	—0.03 (0.86)	0.03 (0.92)	—0.36 (0.16)	—0.16 (0.55)	0.66 (<0.001)	—0.20 (0.16)	—0.30 (0.04)
RWT	0.00 (0.99)	—0.02 (0.89)	0.13 (0.51)	0.19 (0.46)	—0.43 (0.09)	—0.00 (0.78)	0.60 (<0.001)	—0.15 (0.30)	—0.20 (0.17)
LV mass	0.16 (0.40)	—0.33 (0.07)	—0.22 (0.25)	—0.17 (0.50)	—0.23 (0.38)	—0.25 (0.34)	0.64 (<0.001)	—0.26 (0.07)	—0.39 (<0.01)
LV mass index	0.34 (0.06)	—0.38 (<0.05)	—0.28 (0.14)	0.08 (0.75)	—0.45 (0.07)	—0.34 (0.18)	0.74 (<0.001)	—0.29 (0.04)	—0.42 (<0.01)
LV mass/height ^{2.7}	0.41 (<0.05)	—0.43 (<0.05)	—0.14 (0.47)	—0.03 (0.93)	—0.45 (0.07)	—0.22 (0.41)	0.71 (<0.001)	—0.34 (0.02)	—0.34 (0.02)
LV work	—0.08 (0.68)	0.40 (<0.05)	0.26 (0.17)	—0.33 (0.19)	0.00 (0.99)	—0.24 (0.36)	—0.11 (0.42)	0.30 (0.04)	0.11 (0.48)
LV work index	—0.16 (0.40)	0.54 (<0.01)	0.37 (<0.05)	—0.19 (0.47)	0.14 (0.59)	—0.10 (0.71)	—0.66 (<0.001)	0.34 (0.02)	0.37 (0.01)

Values are Pearson correlation coefficients, and corresponding *P* values are in parentheses; *r* (*P*). PWT, posterior wall thickness; ST, septum thickness; TLVD, transverse LV diameter. Bold values are significant at least at level *P* < 0.05.

MBF. The measured basal MBF was similar between the groups, but normalized (LV work index) basal MBF was significantly higher in the ET group than that in the UT group. During adenosine-induced hyperemia, both measured and MAP-normalized MBF were significantly lower and coronary vascular resistance was higher in the ET group than those in the UT group. MBF reserve determined using the normalized MBF values was significantly lower in the ET group than that in the UT group. We also calculated the whole LV wall blood flow by multiplying the measured MBF values with LV mass, and it was significantly higher in the resting state in the ET group than that in the UT group but similar between the groups during adenosine infusion. When age was used as a covariate, all significant differences remained. When LV mass/height^{2.7} was used as a covariate, normalized basal MBF was still significantly higher in the ET group than that in the UT group. However, measured and MAP-normalized hyperemic MBF and coronary vascular resistance were not different between the groups anymore. Because of significantly lower basal MBF, MBF reserve was still significantly lower in the ET group than that in the UT group despite this adjustment (Table 3).

Correlation between MBF and echocardiographical findings. Table 4 shows the correlations between $\dot{V}O_{2\text{peak}}$, measured basal and hyperemic MBF, and different echocardiographical parameters in both groups combined and separately. Both groups combined, $\dot{V}O_{2\text{peak}}$ correlated inversely with basal (*P* = 0.06) and hyperemic MBF (*P* < 0.01). $\dot{V}O_{2\text{peak}}$ correlated positively with most of the structural echocardiographical parameters as well as LV mass, LV mass index, and LV mass/height^{2.7}. Basal and hyperemic MBF correlated mainly negatively with the echocardiographical parameters. When age was used as covariate, all significant correlations with hyperemic MBF remained or became even stronger and most of those with basal MBF became significant (data not shown). On the other hand, when LV mass/height^{2.7} was used as partial correlate, the significant correlation between $\dot{V}O_{2\text{peak}}$ and hyperemic MBF disappeared (*r* = −0.25, *P* = 0.10).

At the group level, $\dot{V}O_{2\text{peak}}$ correlated negatively and significantly with basal MBF in the UT group and with hyperemic MBF in the ET group (Fig. 1). In addition, LV mass and LV mass index correlated similarly and negatively with basal MBF in both groups, although the only significant correlation was between basal MBF and LV mass index and LV mass/height^{2.7} in the ET group. In the ET group, this correlation seemed to be mainly due to increased LV cavity size and not with wall thickening because both basal and adenosine-stimulated MBF correlated significantly with LV diameter, but not with wall thickness, during diastole. When LV mass/height^{2.7} was used as a partial correlate, correlation between $\dot{V}O_{2\text{peak}}$ and hyperemic MBF remained significant (*r* = −0.37, *P* = 0.047) and correlation between $\dot{V}O_{2\text{peak}}$ and basal MBF in UT became even stronger (*r* = −0.59, *P* = 0.02).

MBF in subgroups of ET group. Because indexed LV mass varied a lot within the ET group, we also compared the

FIGURE 1—The associations of basal (A) and hyperemic (B) MBF to $\dot{V}O_{2peak}$ in UT (open circles) and ET (filled circles) subjects.

results within the three subgroups according to the LV mass/height^{2.7} ($ET_1 \leq 60$, $n = 10$; $ET_2 = 60-70$, $n = 12$; $ET_3 > 70$, $n = 9$). These subgroups did not differ from each other in any other demographic parameters, except that those in ET_2 were older than those in the UT group and those in ET_1 had lower BMI than those in the UT group. $\dot{V}O_{2peak}$ did not differ significantly between ET groups (59 ± 4 , 59 ± 4 , and 63 ± 5 mL·g⁻¹·min⁻¹; $P = 0.11$). Because age and BMI differed between the groups, they were taken as covariates in ANCOVA in the following analyses. Normalized basal MBF was significantly higher in all ET subgroups than that in the UT group (UT, 0.58 ± 0.14 ; ET_1 , 0.87 ± 0.29 ; ET_2 , 0.89 ± 0.29 ; ET_3 , 0.83 ± 0.14 ; $P < 0.02$ between UT and ET subgroups). Correspondingly, normalized hyperemic MBF was significantly lower in all ET subgroups than that in the UT group (UT, 3.93 ± 1.36 ; ET_1 , 2.94 ± 0.68 ; ET_2 , 2.62 ± 1.25 ; ET_3 , 2.82 ± 0.66 ; $P < 0.02$ between UT and ET subgroups).

DISCUSSION

The present study was conducted to investigate the association between $\dot{V}O_{2peak}$ and MBF in ET and UT subjects and whether the degree of LV hypertrophy associates to these variables. We found that ET males with significantly higher $\dot{V}O_{2peak}$ had decreased hyperemic MBF compared with that of UT male subjects. Furthermore, we observed that this decreased hyperemic MBF was inversely related to LV mass and the difference between the groups disappeared when the LV mass differences were controlled for.

The ET subjects had an increased SV but similar ejection fraction and cardiac output at rest compared with those of UT subjects. These are normal and comparable findings with those of several earlier reports (36). In addition, the ET subjects demonstrated significantly increased wall thicknesses and, thereby, increased LV mass compared with those of the UT subjects. The average LV mass (330 g) and LV mass index (169 g·m⁻²) in trained subjects are among the highest values reported earlier (1,13). We also found a strong association between LV variables and $\dot{V}O_{2peak}$, as observed in earlier studies (1,36,41) when both groups were pooled together. In the subgroup analysis of the ET group, the trained subjects with the highest LV mass (or wall thickness) did not have superior $\dot{V}O_{2peak}$ compared with that of the trained subjects with much lower mass. This indicates that pronounced myocardial hypertrophy is not a necessary adaptation to achieve a high $\dot{V}O_{2peak}$ in trained subjects, as also suggested earlier (31), but has significant effect on myocardial vascular function, as suggested in the present study.

Basal MBF was similar in both groups, which is also in line with some (17,32,43) but not all previous investigations (13,18). We also observed that the total LV work was similar between the ET and UT subjects, but when LV work was normalized with LV mass (LV work index), the relative LV work was almost 40% lower in the ET group. However, although cardiovascular resistance is increased in athletes aiming to limit myocardial overperfusion (12,13) (oxygen supply vs demand), an athlete's heart seems to be at least slightly luxuriously perfused at rest, as basal MBF normalized for LV work was significantly higher in athletes. This reasoning is based on the fact that LV work is normally closely coupled with oxygen consumption and myocardial perfusion.

During adenosine infusion, the ET group had, on average, 23% lower absolute hyperemic myocardial perfusion than that in the UT group. This is in accordance with the studies by Heiss et al. (47) and Heinonen et al. (13), whereas some other investigations have observed both unchanged (17,32) or increased (18,43) hyperemic perfusion in endurance athletes. We have previously shown an inverse relation between hyperemic MBF and exercise performance (maximal power output during cycling) in highly trained cross-country skiers with pronounced cardiac hypertrophy (13). In the present study, $\dot{V}O_{2peak}$ was inversely related to hyperemic perfusion not only in the entire study population but also in the ET group alone. Moreover, when the group comparisons were also adjusted for age (Table 3), the results remained essentially similar. First, this observation suggests that endurance training diminishes the pharmacologically induced hyperemic blood flow. Second, it also highlights the importance of controlling for aerobic power when studying myocardial reactivity in healthy subjects. Indeed, when the association between $\dot{V}O_{2peak}$ and hyperemic blood flow was controlled for LV mass, both the group difference and correlation (both groups combined) were not significant anymore. On the other hand, within the ET group, correlation remained significant despite this adjustment.

The major finding in the present study was that the ET group had significantly lower hyperemic MBF compared with that in the UT group. This finding is similar with that observed in many pathophysiological states, e.g., in hypertension (20) and in hypertrophic cardiomyopathy (HCM) (19), in which reduced hyperemic MBF or perfusion reserve has been observed (4,22). In addition, our observation of higher perfusion resistance in ET subjects during hyperemic conditions is in line with the results from Knaapen et al. (19), as performed with HCM patients. This suggests that the reduced hyperemic MBF is due to higher extravascular compressive forces. Because many anatomical changes in HCM are similar with those observed in *athlete's heart* (6), one can hypothesize that these changes would also be related to decreased perfusion reserve in ET subjects. In this regard, we found a trend toward a lower reserve in ET men, as measured in absolute terms. When the blood flow reserve was calculated as a ratio between MAP-normalized hyperemic and work-normalized basal blood flow, ET subjects demonstrated almost 50% lower reserve. Consequently, the alteration in hyperemic MBF in ET subjects with very pronounced LV hypertrophy may also have physiological or even clinical significance, but further research is warranted to investigate this possibility.

Mechanistically, it has been suggested that the reduced capillary density, which accompanies the increased LV mass, induces microvascular dysfunction in HCM (21,37). Myocardial perfusion measures, especially during hyperemia as also determined in the present study, serve as a noninvasive functional surrogate for capillary density (4). Studies in healthy animals have proposed that endurance training leads to increased density of coronary arterioles (3,46), whereas capillary density remains largely unchanged (3,26) when cardiac hypertrophy remains minor. However, capillary density can also be decreased even in healthy animals when training has induced marked cardiac hypertrophy (3,46). Furthermore, although the size of coronary arteries is usually closely associated to the LV mass in healthy humans (9), evidence that the growth or enlargement of coronary vasculature does not necessarily always follow the rate of increase in myocardial mass exists (34), which may explain the finding of decreased hyperemic blood flow with increasing LV mass in the present study.

Importantly, rather than associated with the so-called concentric hypertrophy that is typical for many pathophysiological cardiac diseases such as hypertension, we found here that decreased hyperemic blood flow correlated negatively with variables that depict eccentric hypertrophy (larger cavity dimension) and not, for example, with RWT that is a good marker of concentric hypertrophy. Eccentric hypertrophy is a

very typical feature for athletes exposed to high-volume loads during their training, like our trained subjects. Eccentric hypertrophy may also be associated with decrease in capillary length density, which is also known to occur as a result of training, leading to cardiac hypertrophy (3). However, although increasing exercise hyperemia pharmacologically has been shown to improve cardiac function (11) and oxygen consumption (16) at near-maximal exercise, our findings do not necessarily mean that athletes with very pronounced hypertrophy are compromised in their cardiac pumping function, let alone experience ischemia even at maximal exercise. The ET subjects we studied reported having never experienced any chest pain or related sensations. In addition, many of them had succeeded well in international competitions such as in different world championships. Accordingly, it seems that despite reduced cardiac hyperemic vasodilator reserve, LV hypertrophy does not lead to greater susceptibility to myocardial ischemia during external stress (27), but fine-tuned regulatory pathways are able to control bodily function so that capacities of any organ are not exceeded even at maximal exertion (28–30).

Finally, in line with our finding of impaired pharmacologically induced hyperemic response, it has also been previously reported that coronary artery blood flow response to reactive hyperemia is decreased in vigorously trained dogs (42). Reactive hyperemia is a widely used procedure also in human peripheral arteries, correlating positively with fitness in healthy but UT subjects (33,39). However, exercise training has been shown to cause dissociation between peripheral flow capacity and maximal aerobic power (14). Thus, these earlier findings and our results strongly support the proposition of “athlete’s paradox” in which highly trained and performing athletes can have even decreased hyperemic responses when assessed by standard determination procedures at resting state (10).

Taken together, the present study supports the findings from the peripheral vasculature of ET subjects that the cardiac vasodilatory capacity is also not improved but can even be reduced, compared with that in UT controls. In particular, MBF during adenosine-induced hyperemia is diminished in ET subjects and this decrease is associated to $\dot{V}O_{2peak}$, and especially the degree of LV hypertrophy.

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