Coronary Vasodilator Capacity and Epicardial Vessel Remodeling in Physiological and Hypertensive Hypertrophy

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Abstract—The aim of this study was to compare resting coronary flow velocity, determinants of myocardial oxygen demand, and coronary vasodilator capacity in subjects with physiological, exercise-induced, and hypertensive left ventricular hypertrophy. Sixteen healthy sedentary men, 16 endurance athletes, and 16 hypertensive subjects (mean±SEM for left ventricular mass index: 94.9±5.5, 184.6±8.4, 154.4±9.5 g/m^2, respectively) were studied by transesophageal and transthoracic Doppler echocardiography. Coronary flow velocity in left anterior descending artery and cross-sectional area of left main artery were assessed at rest and during dipyridamole-induced vasodilation. Myocardial oxygen demand was estimated through rate-pressure product, left ventricular wall stress, and inotropic function. Coronary flow reserve and minimum coronary resistance were comparable to those of sedentary men in athletes (mean±SEM: 3.23±0.16 versus 3.60±0.18 and 0.96±0.06 versus 1.04±0.04 mm Hg · s · cm^{-1}), while in hypertensive subjects they were decreased and increased, respectively (mean±SEM: 2.31±0.08 and 1.21±0.10 mm Hg · s · cm^{-1}; $P<0.05$ for both). Resting flow velocity was directly related to rate-pressure product in sedentary men and athletes and also to wall stress in athletes, while these correlations were absent in hypertensives. Dilation of left main artery after dipyridamole was significantly higher in athletes than in sedentary men and hypertensive subjects (mean±SEM for area change: 32.9±3.7% versus 12.8±2.5% and 6.4±3.3%; $P<0.05$ and 0.01). These data indicate that vasodilator capacity of coronary microcirculation is not impaired in athletes with physiological hypertrophy, in contrast to hypertensive patients. The relationship between resting flow velocity and determinants of oxygen demand is preserved in physiological hypertrophy but missing in hypertensive hypertrophy. Furthermore, the vasodilator capacity of coronary macrocirculation is also enhanced in exercise-trained subjects. **(*Hypertension*. 2000;36:343-349.)**

Key Words: hypertrophy, left ventricular ■ circulation ■ exercise ■ aging

Left ventricular hypertrophy (LVH) represents an adaptive mechanism by which the heart normalizes wall stress and preserves left ventricular (LV) function. Both systemic hypertension and chronic exercise training may induce LVH. While hypertensive LVH represents a risk factor for cardiovascular morbidity and mortality[1] and is associated with an impairment in coronary vasodilator capacity,[2,3] chronic exercise training is supposed to improve cardiovascular capacity and to reduce morbidity and mortality.[4,5] Experimental studies suggest an exercise-induced protective adaptation in coronary circulation, which may include both structural changes[6,7] and changes in vasomotor responses.[8–10] It was demonstrated that in normotensive animals, such as rat,[11,12] dog,[13] and swine,[7] chronic exercise training results in an improvement of coronary vasodilator reserve. By contrast, studies comparing coronary vasodilator capacity in hypertensive patients with LVH and physically trained subjects with similar age and LV mass are not available.

The present study was designed to compare coronary function, including resting coronary flow and its determinants, vasodilator capacity of conductive and resistive coronary vessels, and remodeling of epicardial vessels in highly trained subjects with physiological LVH, hypertensive subjects with a similar degree of LVH, and healthy sedentary men with normal LV mass. In addition, the effect of aging on coronary vasodilator capacity was compared between hypertensive and exercise-trained subjects.

Methods

Study Population

The study population consisted of 48 subjects, all men: 16 healthy, untrained volunteers (aged 18 to 62 years), 16 endurance athletes (marathon runners and triathletes) with mild to moderate LVH (aged 20 to 79 years), and 16 hypertensive subjects with mild to moderate LVH (aged 41 to 68 years). The mean duration of exercise conditioning in athletes was 28±15 years. LVH in hypertensive subjects and athletes was defined as LV mass index value of 117 g/m^2.[14]

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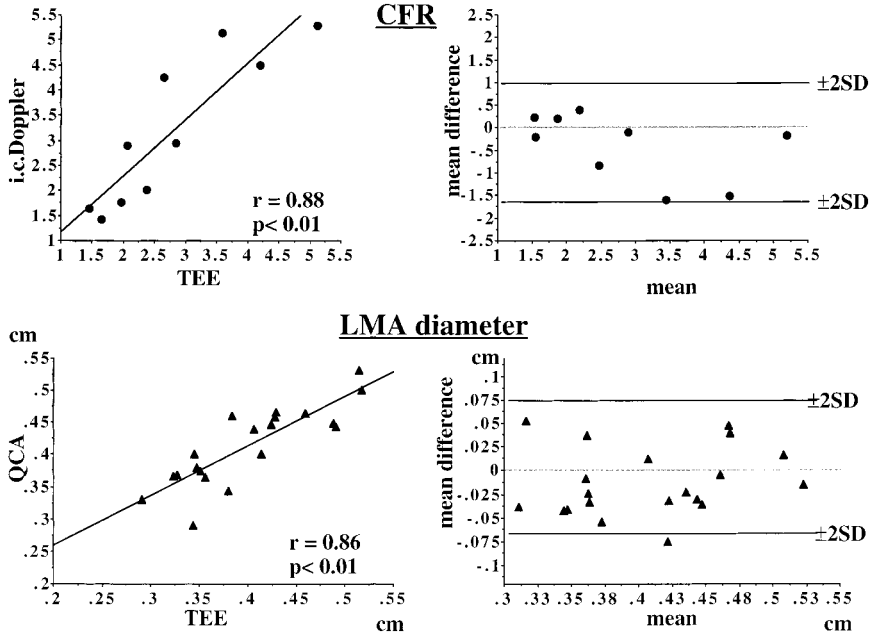

Figure 1. Validation of TEE Doppler against intracoronary (i.c.) Doppler guidewire for the assessment of CFR (top) shows a good correlation and a mean difference of -0.41 ± 0.70 cm/s, with all points within ± 2 SD. Validation of TEE against quantitative coronary angiography (QCA) for LMA diameter (bottom) also shows adequate correlation and a mean difference of $+0.1 \pm 0.35$ mm, with all points but 1 within ± 2 SD.

Coronary artery disease, valvular or primary myocardial heart disease, diabetes, and dyslipidemia were ruled out. None of the controls and athletes was receiving any therapy at the time of the study; in hypertensive patients, calcium antagonists were discontinued at least 72 hours before the study, and all other medications had been stopped for at least 1 week. The study was approved by the internal ethics committee, and all participants provided informed consent according to the Declaration of Helsinki.

Study Protocol

The proximal part of the left anterior descending artery (LAD) was visualized from the upper esophagus by a transesophageal approach, according to a previously described procedure.[15] Blood flow was detected by color and spectral Doppler, and basal coronary flow velocity recording was acquired (SONOS 2500, Hewlett-Packard Co). Digitized "zoomed" 2-dimensional images of the left main coronary artery (LMA) were stored for diameter measurement.

To assess LV wall stress and inotropic function, the probe was briefly advanced to the stomach, and transgastric short-axis view of the left ventricle at the level of papillary muscle was acquired (in both 2-dimensional and M-mode images). Subsequently, the probe was withdrawn to the upper esophagus, and the Doppler signal from LAD was obtained again. Basal coronary flow velocity was remeasured, and high-dose infusion of dipyridamole (0.84 mg/kg for 9 minutes) was started through an indwelling 18-gauge cannula in an antecubital vein. The Doppler signal from the LAD was recorded continuously during dipyridamole infusion and for 8 minutes afterward. Flow velocity was measured by pulsed Doppler; when the velocity exceeded the Doppler limit, continuous-wave Doppler was used. The LMA diameter was remeasured at the maximal flow response. At the end of the study, aminophylline 80 mg was injected in bolus to antagonize the effects of dipyridamole.

Throughout the study, 3-lead ECG and blood pressure (Finapres; Ohmeda) were continuously monitored, and 12-lead ECG was recorded every 2 minutes.

Echocardiographic Indices

LV mass, peak systolic wall stress (PSWS) (pascals), end-systolic wall stress (ESWS) (pascals), and midwall fractional shortening (MFS) (%) were calculated according to the corresponding formulas.[16–18] The measurements necessary for calculations were obtained from M-mode images of the left ventricle in transthoracic parasternal (for LV mass) or transesophageal transgastric (for PSWS, ESWS, and MFS) view. Triple product (TP) (mm Hg · bpm · g) was calculated by multiplying rate-pressure product (RPP) by LV mass.

Coronary Blood Flow Velocity Measurement

The average of instantaneous spectral peak velocities during cardiac cycle (APV) (cm/s) was measured rather than peak diastolic velocity because it better corresponds to volume flow rate.[19] The reproducibility of these measurements was proven in previous studies.[15,20] The mean of 5 beats was used for statistical analysis.

The maximal coronary vasodilator response to dipyridamole was assessed as both coronary flow reserve (CFR) and minimum coronary vascular resistance (MCR) (mm Hg · s · cm^{-1}) and calculated according to the corresponding formulas.[15] Furthermore, the ratio of resting coronary vascular resistance (CVR) to MCR (ie, resistance ratio [RR]) and the percent change from resting CVR to MCR (ΔCVR) (%) were calculated. The accuracy of transesophageal echocardiography (TEE) Doppler for the assessment of coronary vasodilator capacity was preliminarily validated against intracoronary Doppler (Flow-wire, Cardiometrics) in a different group of 10 hypertensive patients undergoing coronary angiography for chest pain. The time interval between TEE and intracoronary Doppler study did not exceed 1 week.

In all study groups, correlations of resting APV with age, LV mass, resting RPP, TP, PSWS, ESWS, and MFS as well as correlation of APV after high-dose dipyridamole with age and LV mass were investigated by means of regression analysis.

Evaluation of Coronary Artery Caliber

LMA diameter was measured basally and during maximal flow response in 2-dimensional images. Measurements were provided by bow compasses from digitized "zoomed" diastolic images at 3 different segments of LMA, and the mean value was used to calculate LMA area. The mean of 5 cardiac cycles was used for statistical analysis. Correlations of LMA area at baseline and after dipyridamole with age and LV mass were investigated by means of regression analysis. The accuracy of TEE for the measurement of epicardial vessel diameter was preliminarily validated against quantitative coronary angiography in a different group of 20 subjects with normal coronary arteries undergoing diagnostic coronary angiography for chest pain.

Data Analysis

Data in the tables are expressed as mean $\pm$1 SEM. ANOVA was used when appropriate. To assess statistical significance between groups,

TABLE 1. Main Vital Characteristics, LV Geometry, and Systolic Function in Study Population

	Sedentary Men	Athletes	Hypertensive Subjects
Age, y	46.5±4.0	53.1±5.0	58.0±2.0
Aged ≥65 y, No. of subjects	0	6	6
SBP before study, mm Hg	136.2±4.0	135.1±4.0	171.2±4.0†§
DBP before study, mm Hg	69.7±2.0	70.4±3.0	103.5±3.0†§
IVS diastolic thickness, mm	9.8 ± 10^{-3}	13.6 ± 10^{-3}†	13.5 ± 10^{-2}†
PW diastolic thickness, mm	9.6 ± 10^{-3}	12.5 ± 10^{-4}†	12.6 ± 10^{-2}†
LV diastolic diameter, mm	49.0±2.0	52.8±1.0	47.7±2.0
LV mass, g	191.4±14.0	348.6±17.3†	297.5±23.5†
LV mass index, g/m^2	94.9±5.5	184.6±8.4†	154.4±9.5†‡
MFS, %	17.6±0.5	16.5±0.4	14.7±0.6*
PSWS · 10^2, Pa	129.0±5.1	102.7±6.8	118.2±10.6
ESWS · 10^2, Pa	53.9±2.9	49.8±3.3	59.2±5.5

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; IVS, interventricular septum; and PW, posterior wall.

*$P<0.05$ vs sedentary men; †$P<0.01$ vs sedentary men; ‡$P<0.05$ vs athletes; §$P<0.01$ vs athletes.

Scheffé's F test was applied, with a value of $P<0.05$ considered significant. Regression analysis was performed with simple linear and multiple stepwise models. Statistical analysis was performed by commonly available software (StatView SE+ Graphics, Abacus Concepts Inc). The agreement between TEE Doppler, intracoronary Doppler, and quantitative coronary angiography, respectively, was assessed according to the Bland-Altman approach.[21]

Results

Validation of the TEE approach for measurement of CFR and LMA diameter against intracoronary Doppler and quantitative coronary angiography, respectively, is presented in Figure 1.

Age and Echocardiographic Measurements

Mean age was comparable between hypertensive subjects and athletes and was slightly lower in healthy sedentary men (Table 1). Elderly subjects were defined as those aged ≥65 years.[22] LV mass and mass index were higher in athletes than in hypertensive subjects ($P<0.05$ for LV mass index) because of slightly higher LV diastolic diameter. MFS was reduced in hypertensive subjects ($P<0.05$ versus sedentary men). No differences between groups were observed for PSWS and ESWS.

Systemic Hemodynamics

Systolic, diastolic, and mean blood pressure measured simultaneously with coronary flow velocity, both at rest and after high-dose dipyridamole, were higher in the hypertensive group (Table 2). Heart rate was lower in athletes than in hypertensive subjects. Resting RPP was higher in hypertensive subjects than in either sedentary men or athletes ($P<0.01$ versus both).

Coronary Blood Flow Velocity Responses

Resting APV of LAD flow was significantly higher in hypertensive subjects than in controls ($P<0.05$) and athletes ($P<0.01$) (Table 3). After administration of dipyridamole, no differences were observed between groups. Thus, in hypertensive subjects MCR was higher and CFR, RR, and ΔCVR were lower than in controls and athletes.

Resting APV was directly related to resting RPP and TP in sedentary men and athletes (Figure 2) but not in hypertensive subjects; in athletes only, it was also related to PSWS ($y=7.0+0.16x$; $r=0.52$, $P<0.05$) and ESWS ($y=3.0+0.41x$; $r=0.65$, $P<0.01$). In stepwise multiple regression analysis, only RPP entered the regression against resting APV in sedentary men and athletes. Both resting and peak APV during dipyridamole were not related to LV mass or age in any group.

TABLE 2. Systemic Hemodynamic Response to Dipyridamole Infusion

	Sedentary Men	Athletes	Hypertensive Subjects
SBP, mm Hg			
Rest	128.5±2.9	132.7±5.0	166.5±5.1†§
Dipyridamole	123.1±3.0	124.4±4.5	142.2±5.1†§
DBP, mm Hg			
Rest	67.4±2.6	68.2±4.0	91.9±3.7†§
Dipyridamole	63.4±3.6	62.3±3.2	75.9±3.0‡
MBP, mm Hg			
Rest	87.6±2.2	88.6±3.9	115.9±3.9†§
Dipyridamole	83.3±3.2	83.0±3.3	98.2±3.3*‡
Heart rate, bpm			
Rest	82±5.0	72±2.0	89±3.0†§
Dipyridamole	107±4.0	88±3.0*	103±4.0‡
RPP, mm Hg · bpm			
Rest	10 648±572	9507±481	14 719±519†§
Dipyridamole	12 986±583	10 795±653	14 897±956‡

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and MBP, mean blood pressure.

*$P<0.05$ vs sedentary men; †$P<0.01$ vs sedentary men; ‡$P<0.05$ vs athletes; §$P<0.01$ vs athletes.

TABLE 3. Coronary Flow Velocity in LAD, Coronary Reserve, Minimum Coronary Resistance, and LMA Area (and Response to Dipyridamole Infusion)

	Sedentary Men	Athletes	Hypertensive Subjects
APV resting, cm/s	28.2±2.0	23.5±2.1	37.7±2.7*§
APV dipyridamole, cm/s	89.9±4.8	82.2±5.3	85.4±5.2
CFR	3.23±0.16	3.60±0.18	2.31±0.08†§
MCR, mm Hg · s · cm^{-1}	0.96±0.06	1.04±0.04	1.21±0.10*
RR	3.48±0.19	3.93±0.16	2.56±0.10†§
ΔCVR, %	69.9±1.7	74.0±1.1*	59.8±1.5†§
LMA area basal, mm^2	12.3±0.9	14.9±0.9	10.9±1.0‡
LMA area dipyridamole, mm^2	13.9±1.1	19.7±1.2†	11.5±1.1§
Increase in LMA area, mm^2	1.62±0.32	4.83±0.62*	0.60±0.39§
Increase in LMA area, %	12.8±2.5	32.9±3.7†	6.4±3.3§

*$P<0.05$ vs sedentary men; †$P<0.01$ vs sedentary men; ‡$P<0.05$ vs athletes; §$P<0.01$ vs athletes.

Response of Coronary Artery Caliber to Dipyridamole

The diameter of the LMA could be measured in 34 subjects (71%) (12 controls, 9 hypertensive subjects, and 13 athletes). LMA cross-sectional area at baseline and after administration of dipyridamole in the 3 groups is represented in Figure 3. In athletes, basal LMA area was slightly increased compared with sedentary men and significantly increased compared with hypertensive subjects ($P<0.05$). Athletes also had significantly enhanced dilation of LMA either as absolute values or percent increase (Table 3). In hypertensive subjects, an inverse relation was observed between age and LMA area ($y=25.3-0.27x$; $r=-0.73$, $P<0.05$). No relationship between LMA area and LV mass was observed in any group.

Effect of Aging on Coronary Flow Velocity at Rest and Coronary Vasodilator Capacity

The effect of aging on coronary circulation was not evaluated in healthy sedentary men since none of them reached the age of 65 years (Table 4). In hypertensive subjects, resting APV was comparable between subjects older and younger than 65 years, despite significant differences in blood pressure and LV wall stress. APV after administration of dipyridamole was lower in older hypertensive subjects, even if measured under higher perfusion pressure, thus resulting in higher MCR and lower CFR, RR, and ΔCVR.

By contrast, older athletes demonstrated higher resting APV, mean blood pressure, RPP, and LV wall stress than younger ones. APV and mean blood pressure after administration of dipyridamole were slightly higher in older athletes. Thus, CFR was significantly lower in older athletes, but MCR, RR, and ΔCVR were comparable in older and younger athletes.

Discussion

To the best of our knowledge, this is the first study comparing the features of coronary circulation in men with physiological, exercise-induced LVH and in hypertensive patients of similar age and LV mass. Detailed information on coronary vasodilator capacity in exercise-induced LVH was obtained in various animal models.[6–8,11–13] However, studies in endurance athletes thus far provided data on morphology and function of LV myocardium[23,24] and size and dilating capacity of large coronary arteries,[24,25] while vasodilator capacity of coronary microcirculation was studied only in small series of young athletes without a control group of hypertensive patients with comparable LVH.[26,27] In this study, we took advantage of an integrated echocardiographic approach that allowed us to assess, in a noninvasive manner, resting coronary flow velocity together with the main determinants of myocardial oxygen demand,[16–18] as well as the response of

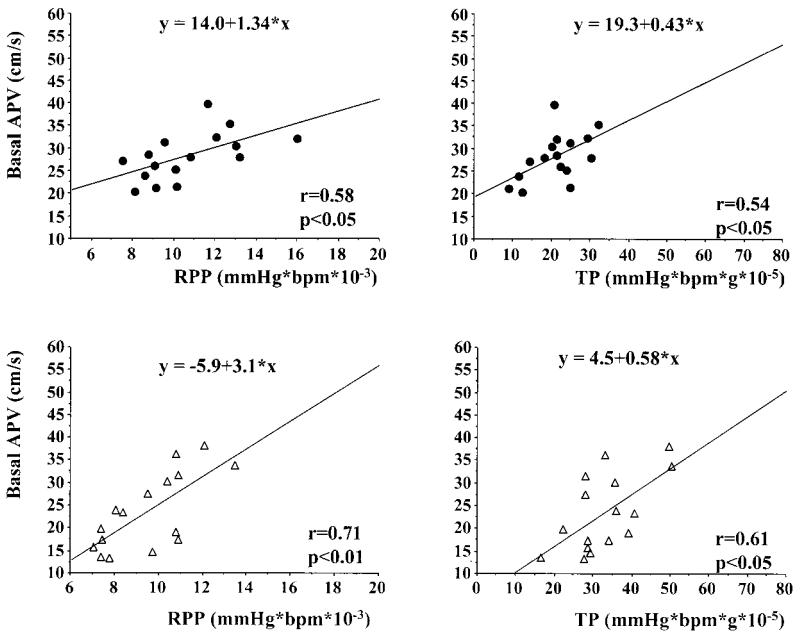

Figure 2. Scatterplots of correlation between basal APV, RPP, and TP in sedentary men (●) and endurance athletes (△).

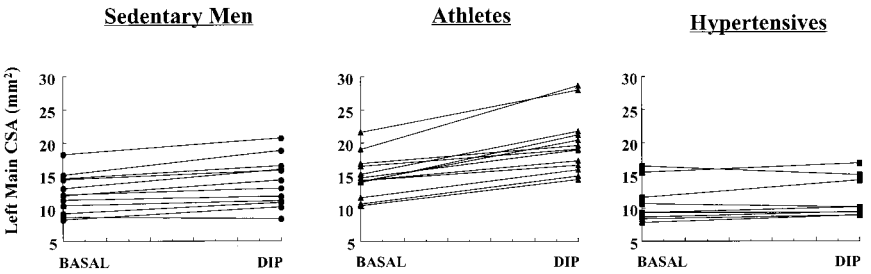

Figure 3. Scatterplot of coronary left main cross-sectional area (CSA) at baseline (BASAL) and after dipyridamole (DIP) in sedentary men, athletes, and hypertensive patients. See also Table 3.

coronary flow velocity and epicardial vessel diameter to intravenous infusion of a vasodilator agent.[15,20]

The main findings of the study are as follows: (1) in hypertensive LVH, the correlation between resting coronary flow velocity and determinants of myocardial oxygen demand is missing, while this relationship is preserved in physiological LVH; (2) maximal coronary vasodilation at the microcirculatory level is preserved in athletes with physiological LVH, while it is impaired in hypertensive LVH; (3) exercise training accompanied by physiological LVH is associated with a favorable remodeling and enhanced vasodilator capacity of the epicardial vessels; and (4) the effect of aging on coronary microcirculation is different between hypertensive subjects with LVH and athletes with physiological LVH.

Altogether, these results suggest that hypertensive disease, but not LVH per se, modifies the simple relationship between resting flow velocity and determinants of resting myocardial oxygen demand and that, as previously reported in exercising pigs,[6] adaptive changes at the microvascular level parallel exercise-induced but not hypertensive LVH. In regard to conduit vessels, exercise training induces a favorable remodeling because of frequent high-flow stimuli caused by a substantial increase in myocardial oxygen demand during exercise load,[24,25] while chronic pressure increment results in hypertensive vascular remodeling with thickening of the medial layer and normal or slightly decreased luminal diameter,[28] with luminal narrowing progressively increasing with age. The enhanced dilating response of LMA to dipyridamole observed in athletes, 3-fold compared with sedentary controls and 5-fold compared with hypertensive patients, can be partially endothelium mediated[29,30] and partially dependent on increased sensitivity of coronary smooth muscle to endothelium-independent vasodilator.[25,31] Mechanisms underlying the age-dependent decrease of CFR are different between athletes and hypertensive subjects: in older athletes the reduction in CFR is primarily due to an increase in basal blood pressure, cardiac work, and flow velocity and not to a

TABLE 4. Effect of Age on Coronary Function and Determinants of Myocardial Oxygen Demand

	Hypertensive Subjects		Athletes	
	<65 Years	≥65 Years	<65 Years	≥65 Years
Rest				
APV, cm/s	36.8±4.1	38.3±6.8	20.5±2.6	28.4±2.6*
MBP, mm Hg	108.5±4.2	128.1±4.4†	83.9±4.8	96.4±5.7
Heart rate, bpm	92.1±4.0	85.8±5.9	72.3±3.0	71.2±4.0
RPP, mm Hg · bpm	14 340±640	15 350±894	8879±586	10 554±688
PSWS, $\cdot 10^2$, Pa	101.9±7.9	145.4±21.9*	94.4±6.9	116.5±12.8
ESWS, $\cdot 10^2$, Pa	50.7±4.9	73.4±10.2*	46.5±4.8	55.4±2.8
MFS, %	14.7±0.8	14.7±1.0	16.2±0.4	16.9±1.0
LV mass, g	274.1±18.3	336.5±54.1	340.6±21.0	361.8±27.6
LMA area, mm^2	11.9±1.4	8.8±0.5	14.9±1.3	14.9±0.9
Dipyridamole				
APV, cm/s	91.8±7.1	74.7±5.4	77.8±6.5	89.5±8.7
MBP, mm Hg	95.6±4.0	104.3±5.5	78.7±3.9	90.2±4.8
LMA area, mm^2	12.5±1.4	9.5±0.4	20.4±1.9	18.5±1.1
CFR	2.47±0.09	2.04±0.06†	3.96±0.20	3.02±0.13†
MCR, mm Hg · s · cm^{-1}	1.08±0.09	1.42±0.10*	1.04±0.05	1.04±0.09
RR	2.70±0.13	2.23±0.09*	4.15±0.19	3.63±0.21
ΔCVR, %	61.9±2.1	55.1±1.6*	75.6±1.2	71.4±1.8
Increase in LMA area, %	5.7±4.7	8.0±4.2	37.6±4.2	25.5±6.0

MBP indicates mean blood pressure.
*$P<0.05$, †$P<0.01$ for ≥65 vs <65 years.

reduced vasodilator capacity. A similar pattern of age-related change in CFR was described for a normal population.[32] In contrast, the further reduction in CFR observed in older hypertensive subjects was the result of a decreased hyperemic flow velocity and increased MCR, suggesting a role of aging in enhancing the impairment of coronary vasodilator capacity in arterial hypertension. Progressive increase in myocardial fibrosis with aging has been proposed as a possible mechanism limiting CFR in experimental models of hypertension.[33]

Study Limitations

TEE Doppler allows measurement of coronary flow velocity in LAD and vessel caliber at the LMA level. Consequently, volumetric flow cannot be assessed by this approach, and microcirculatory function must be evaluated through the flow velocity response to an arteriolar vasodilator. Actually, Wangler et al[34] and Marcus et al[35] demonstrated that changes in coronary blood flow velocity are closely correlated with changes in microsphere-measured myocardial perfusion, thus representing a good index of CFR, and we validated our TEE Doppler flow velocity measurements against those by intracoronary Doppler guidewire. The LMA diameter in this study was measured not to extrapolate volumetric flow but as an optimal window to assess remodeling and vasodilator capacity of epicardial coronary artery. Measurement of LMA diameter by the TEE approach shows relatively lower feasibility than Doppler recording of coronary flow; however, our validation of TEE against quantitative coronary angiography shows good accuracy of the measurement, when feasible, in keeping with the findings of Hildick-Smith and Shapiro[36] using transthoracic echocardiography.

Conclusions

In contrast to findings in hypertensive patients with LVH, exercise-induced, physiological LVH in athletes of comparable age is associated with enhanced vasodilator capacity of coronary conductance vessels and preserved vasodilator capacity at the resistance artery level. In addition, the relationships between resting flow velocity and determinants of myocardial oxygen demand are preserved in exercise-induced but not in hypertensive LVH. These data indicate that LVH per se does not necessarily imply an impairment in flow-function coupling and coronary vasodilator capacity. Furthermore, the effect of aging on arteriolar vasodilator capacity seems to be different in hypertensive and physiological LVH.

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