Coronary Artery Dimensions in Primary and Secondary Left Ventricular Hypertrophy

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Background. Coronary artery enlargement has been previously described in left ventricular hypertrophy.

Objectives. We sought to assess coronary artery dimensions and their relation to left ventricular muscle mass in primary and secondary hypertrophy.

Methods. Cross-sectional area of the left and right coronary arteries was determined by quantitative coronary angiography in 52 patients: 12 control subjects and 40 patients (13 with hypertrophic cardiomyopathy, 12 with dilated cardiomyopathy and 15 with aortic valve disease). As a measure of left ventricular hypertrophy, angiographic left ventricular mass and equatorial cross-sectional muscle area were determined.

Results. Cross-sectional area of both the left and right coronary arteries is increased in left ventricular hypertrophy (p < 0.05 vs. values in control subjects). There is a curvilinear relation between left coronary artery size and left ventricular muscle mass (r = 0.76) or cross-sectional muscle area (r = 0.75). However, normalization of coronary cross-sectional area for left ventricular muscle mass or muscle area shows insufficient enlargement of the coronary arteries in both primary and secondary hypertrophy.

Conclusions. 1) Coronary artery size increases as left ventricular mass increases in both primary and secondary hypertrophy. 2) The enlargement of left coronary cross-sectional area is independent of the cause of the increase in left ventricular mass. 3) The size of the coronary arteries is inappropriate with regard to left ventricular hypertrophy. Thus, the stimulus for growth of the coronary arteries is not influenced by the underlying disease but appears to depend on the degree of left ventricular hypertrophy.

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Enlargement of the coronary arteries has been reported in patients with left ventricular hypertrophy at necropsy (1,2) and in clinical studies (3-5). Increased dimensions of the left anterior descending and circumflex coronary arteries were found in patients with left ventricular hypertrophy secondary to aortic or mitral valve disease as well as in patients with hypertension (3-14). In severe left ventricular hypertrophy the coronary arteries have limited ability to grow (3,5) and thus carry the risk of underperfusion during high demand situations such as physical exercise. However, the regulatory mechanisms are largely unknown and may be different in primary and secondary as well as eccentric and concentric hypertrophy. Thus, the purpose of the present study was to analyze coronary artery size in patients with dilated and hypertrophic cardiomyopathy, and to compare the results with previously reported data in patients with secondary left ventricular hypertrophy (4).

Methods

Patients. Twelve patients with atypical chest pain and normal coronary arteries served as control subjects (group 1,

mean age ± SD 52 ± 8 years, nine men and three women). These patients had no valvular or coronary artery disease or left ventricular hypertrophy. The remaining 40 patients comprised 13 patients with hypertrophic cardiomyopathy (group 2, mean age 43 ± 9 years, 10 men and 3 women), 12 patients with dilated cardiomyopathy (group 3, mean age 52 ± 9 years, 7 men and 5 women) and 15 patients with aortic valve disease (group 4, mean age 55 ± 7 years, 12 men and 3 women). Functional classification was assessed according to New York Heart Association criteria.

Cardiac catheterization. Patients underwent right and left heart catheterization for diagnostic purposes. Informed consent was obtained from all patients. Premedication consisted of chlordiazepoxide, 10 mg, administered orally 1 h before the procedure. Vasoactive substances were withheld for 24 h before catheterization. Aortic pressure was measured with an 8F pigtail catheter introduced retrogradely from the right femoral artery and pulmonary artery pressure with a 7F Cournand catheter from the right femoral vein. After left ventricular angiography, diagnostic coronary arteriography was carried out by the Judkins technique. A nonionic contrast material (iopamidoltrometamol; Lopamiro 370) was used for quantitative coronary angiography to minimize hyperemic reactions with transient changes in coronary blood flow (15). Cine film was used as a data carrier (filming rate 50 frames/s).

Left ventricular volume and ejection fraction were calculated according to the area-length method (16). Left ventricu-

lar muscle mass was determined with the formula of Rackley et al. (17). In patients with hypertrophic cardiomyopathy and asymmetric hypertrophy, cross-sectional muscle area at the left ventricular equator (LVMA [cm^2]) was used as a measure of left ventricular hypertrophy:

$$LVMA = \pi(M/2 + h)^2 - \pi(M/2)^2,$$

where M = left ventricular angiographic short-axis diameter; and h = left ventricular angiographic wall thickness measured in the right anterior oblique projection. For comparison purposes, this variable was also calculated in all other patients. In patients with hypertrophic cardiomyopathy, wall thickness (h$_c$) was calculated from the angiographic thickness multiplied by the echocardiographic septal/posterior wall thickness ratio (s/p) to correct for asymmetric septal hypertrophy:

$$h_c = [h + (h \cdot s/p)]/2.$$

Quantitative coronary arteriography. Quantitative evaluation of coronary arteriograms was performed with a semiautomatic computer system (18). For each vessel segment, two to three end-diastolic measurements in different projections were carried out and averaged to correct for biologic variations in coronary artery dimensions (19,20). The computer system is based on a 35-mm film projector (Tagarno A/S, Horsens, Denmark), a slow scan charged coupled device camera (for image digitation) developed at the Institute for Biomedical Engineering in Zurich, and a computer workstation (Apollo DN 3000, Apollo Computer AG, Wangen, Switzerland) for image storage and processing. Contour detection was carried out by using a geometric-densitometric edge detection algorithm (21–24).

The methodology for computerized analysis of coronary arteriograms has been described elsewhere (18). Briefly, a three-dimensional model of the vessel was constructed by matching center lines of the individual biplane tracings. By digitizing the angiograms with a resolution of 1,024 by 1,368 pixels, a spatial resolution of 0.1 mm in the heart can be obtained. The gray scale range of 12 bits corresponds to the dynamic range of the X-ray film, allowing for a highly reproducible and accurate lumen identification even on low contrast images. Phantom measurements with a Plexiglas model showed excellent correlations between the true and the measured diameter (r = 0.99). The mean difference (= accuracy) amounted to 0.02 mm for both planes and the standard deviation of difference (= precision) was 0.09 mm for plane A and 0.12 mm for plane B, respectively. Intraobserver and interobserver variability were small (SEE [biplane data] 0.072 mm^2 [2.1% of the mean vessel area] and 0.14 mm^2 [4.1% of the mean vessel area] for intraobserver and interobserver variability) (18).

The proximal cross-sectional area of the three major coronary vessels (left anterior descending, left circumflex and right coronary artery) was measured in all patients. The proximal cross-sectional area of the left anterior descending and left circumflex arteries was defined as the vessel segment immediately beyond the bifurcation of the left main coronary artery

Table 1. Hemodynamic and Angiographic Data

	Control Subjects (n = 12)	Patients With Cardiomyopathy	
		Hypertrophic (n = 13)	Dilated (n = 12)
LVSP (mm Hg)	114 ± 20	161 ± 36‡	112 ± 23‖
LVEDP (mm Hg)	9 ± 4	20 ± 7†	15 ± 8
MPAP (mm Hg)	15 ± 3	18 ± 5	18 ± 7
EF (%)	65 ± 4	75 ± 7*	29 ± 12‡‖
EDV (ml)	137 ± 28	166 ± 38	347 ± 193‡§
LMM (g)	123 ± 29	—	318 ± 189
LVMA (cm)	18 ± 7	33 ± 7†	28 ± 8*

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ versus control subjects; §$p < 0.01$, ‖$p < 0.001$ versus patients with hypertrophic cardiomyopathy. Data presented are mean value ± SD. EDV = end-diastolic volume; EF = ejection fraction; LMM = left ventricular muscle mass; LVEDP = left ventricular end-diastolic pressure; LVMA = cross-sectional muscle area at the left ventricular equator; LVSP = left ventricular systolic pressure; MPAP = mean pulmonary artery pressure.

over a length of ~1 cm. The computer traced this segment automatically and calculated the mean area over this segment. The proximal cross-sectional area of the right coronary artery was defined as the vessel segment 1 to 2 cm distal to the coronary ostium. A vessel segment was analyzed over a length of 1 cm, and the mean cross-sectional area was calculated as for the left coronary artery. Calibration was performed automatically by using the proximal part of the 8F Judkins catheter as a scaling device (20,25). As index of the enlargement of the coronary arteries with respect to muscle mass, the cross-sectional area of the left coronary artery (left anterior descending artery plus left circumflex artery) per 100 g of angiographic mass was calculated. In patients with hypertrophic cardiomyopathy (and in all others) coronary artery dimensions were normalized to cross-sectional muscle area at the left ventricular equator.

Statistical analysis. Hemodynamic and angiographic data were compared by a one-way analysis of variance. When the analysis was significant, the Tukey test was applied. Linear regression analysis was performed by using the least squares technique. Data are reported as mean value ± 1 SD.

Results

Hemodynamic, clinical and angiographic data. Of the 13 patients with hypertrophic cardiomyopathy, 10 were classified preoperatively in functional class II and 3 in class III. Six of the 12 patients with dilated cardiomyopathy were in functional class II, 4 in class III and 2 in class IV. Hemodynamic and angiographic data in control subjects and patients with primary hypertrophy are reported in Table 1. Data from patients with secondary hypertrophy are not included because they have been reported previously (4). In patients with hypertrophic cardiomyopathy, the peak systolic pressure gradient was 33 ± 25 mm Hg at rest, 107 ± 34 mm Hg during postextrasystolic beats and 78 ± 28 during the Valsalva maneuver. Mitral regurgitation fraction as assessed by the angio-Fick method was 19 ± 9%. Left ventricular ejection fraction was 75% and

Table 2. Quantitative Coronary Arteriographic Data

	Control Subjects (n = 12)	Patients With Cardiomyopathy	
		Hypertrophic (n = 13)	Dilated (n = 12)
CSA_{LAD}	7.8 ± 3.6	13.5 ± 2.6‡	12.0 ± 4.2‡
CSA_{LCx}	6.7 ± 3.2	11.6 ± 3.0‡	10.6 ± 3.7‡
CSA_{RCA}	9.0 ± 4.7	12.2 ± 2.9*	14.3 ± 5.6‡
f_1 (mm²/100 g)	11.5 ± 5.8	—	7.1 ± 1.5†
f_2 (mm²/cm²)	0.92 ± 0.63	0.83 ± 0.13*	—

*p < 0.05, †p < 0.01, ‡p < 0.005 versus control subjects. Data presented are mean value ± SD. CSA_{LAD} = cross-sectional area of the left anterior descending coronary artery; CSA_{LCx} = cross-sectional area of the left circumflex coronary artery; CSA_{RCA} = cross-sectional area of the right coronary artery; f_1 = [(CSA_{LAD} + CSA_{LCx})/Left ventricular muscle mass × 100; f_2 = [(CSA_{LAD} + CSA_{LCx})/Short-axis equatorial cross-sectional area of the left ventricle.

29%, respectively, in patients with hypertrophic or dilated cardiomyopathy (p < 0.001). Left ventricular end-diastolic pressure was significantly higher than control values in patients with hypertrophic cardiomyopathy, but not in those with dilated cardiomyopathy. Left ventricular muscle mass was increased to 318 ± 189 g in patients with dilated cardiomyopathy and to 307 ± 72 g in those with aortic valve disease. Left ventricular mass was 125 ± 29 g in control subjects (p < 0.01 vs. patients with dilated cardiomyopathy and those with aortic valve disease). Cross-sectional muscle area was 33.0 ± 6.6 cm² in patients with hypertrophic cardiomyopathy, 28.4 ± 8.2 cm² in those with dilated cardiomyopathy, 29.8 ± 6.5 in those with aortic valve disease and 17.7 ± 6.9 cm² in control subjects (all p < 0.001 vs. control subjects).

Coronary artery dimensions. Coronary angiographic data are summarized in Table 2. In patients with dilated and hypertrophic cardiomyopathy, the left and right coronary arteries were larger than those in control subjects (Fig. 1). However, normalized coronary cross-sectional area per 100 g muscle mass (left anterior descending plus left circumflex coronary artery) was significantly lower (Fig. 2) in patients with

Figure 1. Cross-sectional area of the left coronary artery in patients with primary and secondary hypertrophy. AI = patients with aortic insufficiency; AS = patients with aortic stenosis; C = control subjects; DCM and HCM = patients with dilated and hypertrophic cardiomyopathy, respectively; LCA = sum of the left anterior descending and circumflex coronary arteries. Data for patients with aortic stenosis and aortic insufficiency are from Villari et al. (4). *p < 0.05 versus control subjects.
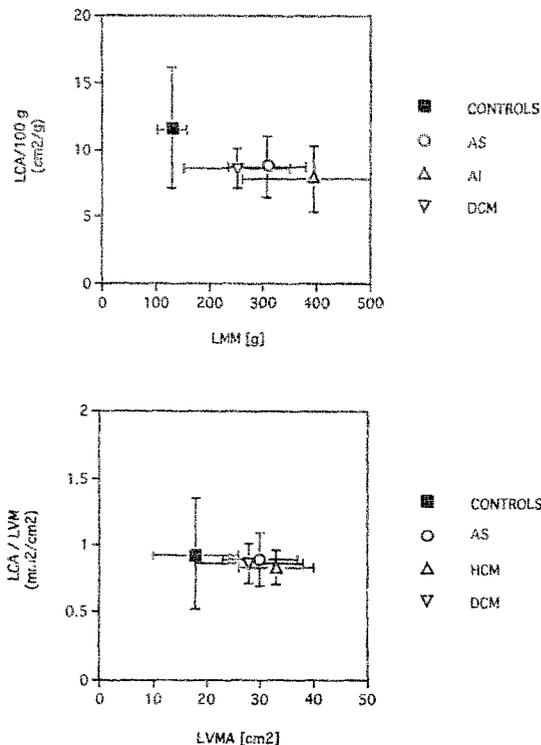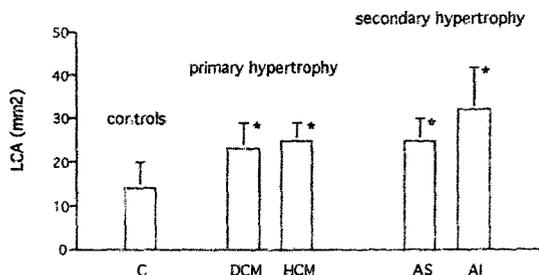

Figure 2. Plot of the left coronary artery dimensions (LCA, mm²) versus (**top panel**) left ventricular muscle mass (LMM) and (**bottom panel**) left ventricular equatorial muscle area (LVMA). There is an inappropriate increase in left coronary artery dimensions in patients with severe left ventricular hypertrophy; that is, a relative decrease in coronary artery size with an increase in mass. Abbreviations as in Figure 1. Data for patients with aortic stenosis and aortic insufficiency are from Villari et al.

dilated cardiomyopathy (7.1 ± 1.5 mm²/100 g) and aortic valve disease (7.9 ± 2.1 mm²/100 g) than in control subjects (11.5 ± 5.8 mm²/100 g, p < 0.05). Similarly, normalized coronary cross-sectional area/1 cm² cross-sectional muscle area was smaller in patients with hypertrophic cardiomyopathy (0.83 ± 0.13 mm²/cm², p < 0.05) than in control subjects (0.92 ± 0.63 mm²/cm²).

Correlations. A significant correlation was found between left coronary artery size and left ventricular end-diastolic volume, left ventricular muscle mass and cross-sectional muscle area (Table 3, Fig. 3). However, left coronary artery size was not correlated with ejection fraction. A correlation was also found between right coronary artery size and mean pulmonary artery pressure (Fig. 4) or left ventricular end-diastolic volume but not with cross-sectional muscle area.

Discussion

In experimental and clinical studies a direct relation between left ventricular muscle mass and coronary dimensions has been reported (6–8,11,26–29). Blood flow velocity has been postulated as a regulatory mechanism. An increase in

Table 3. Correlation Between Coronary Artery Dimensions and Hemodynamic Variables

Variable	Left Coronary Artery (n = 35)		Right Coronary Artery (n = 37)	
	r Coeff	p Value*	r Coeff	p Value*
LVSP (mm Hg)	0.075	0.670	0.02	0.90
LVEDP (mm Hg)	0.45	0.007	0.19	0.25
MPAP (mm Hg)	0.31	0.07	0.38	0.019
EF (%)	−0.14	0.42	−0.291	0.08
LVEDV (ml)	0.42	0.012	0.371	0.024
LMM (g)	0.72	0.0002 (n = 21)	0.44	0.037
LVMA (cm²)	0.75	0.0001 (n = 26)	0.30	0.117

*Linear regression analysis. Coeff = coefficient; other abbreviations as in Table 1.

mean flow velocity has been associated with a change in shear stress, which has been shown to be a mediator for the release of the endothelium-derived relaxing factor, the putative nitric oxide. Endothelium-derived relaxing factor is a potent vasodi-

Figure 3. Correlation between left coronary artery cross-sectional area (LCA) and left ventricular muscle mass (LMM) **(top panel)** and left ventricular cross-sectional muscle area (LVMA) **(bottom panel)**. The curvilinear relation was better than the linear relation. Data for patients with aortic stenosis are from Villari et al. (4). Abbreviations as in Figure 1.
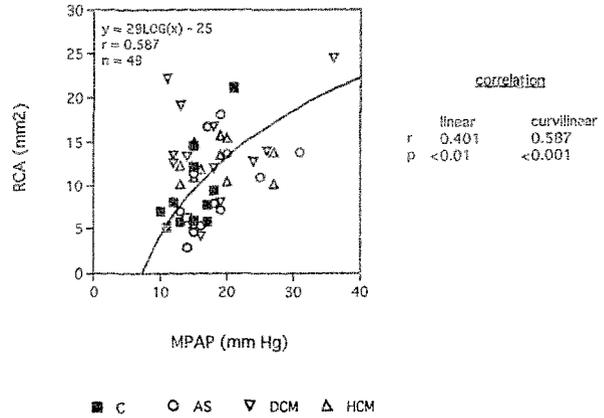

Figure 4. Correlation between right coronary artery cross-sectional area (RCA) and mean pulmonary artery pressure (MPAP). The curvilinear relation was better than the linear relation. Data for patients with aortic stenosis are from Villari et al. (4). Abbreviations as in Figure 1.
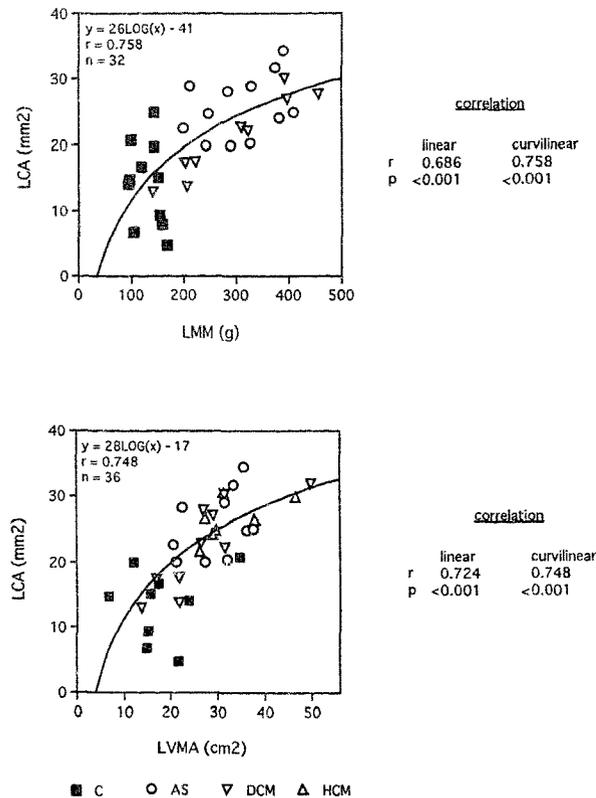
lator and is responsible for the regulation of coronary artery size, during exercise, for example. In low and moderate grades of left ventricular hypertrophy an appropriate increase in coronary artery size has been reported, whereas in severe left ventricular hypertrophy an inappropriate growth of the coronary arteries with a reduction in cross-sectional vessel area/100 g muscle mass has been noted (4).

Coronary artery dimensions in primary and secondary hypertrophy. In the present study, coronary artery dimensions in patients with primary hypertrophy were analyzed and compared with those in patients with secondary hypertrophy due to aortic valve disease (Fig. 1). In both hypertrophic and dilated cardiomyopathy, we observed a large increase in coronary artery size that was independent of the cause and insufficient for the degree of left ventricular hypertrophy. There was a curvilinear relation between left coronary artery size and left ventricular hypertrophy (muscle mass and area, respectively) (Fig. 3); that is, the slope of this relation becomes asymptomatic with large masses and, thus, the ratio between cross-sectional area and muscle mass decreases (Table 2). Thus, patients with primary and secondary hypertrophy demonstrate an inadequate growth of the coronary artery with regard to the increase in left ventricular mass; that is, in severe hypertrophy the coronary arteries are too small for the increase in left ventricular muscle mass.

Pathophysiologic considerations. Although the size of the coronary arteries is not a limiting factor for myocardial perfusion, functional adaptation by way of the release of endothelium-derived relaxing factor seems to be inadequate in severe hypertrophy. An insufficient growth of the coronary arteries has been observed in severe left ventricular hypertrophy (5) and may explain the occurrence of myocardial ischemia in high demand situations such as exercise.

The exact mechanism of controlling the growth of the coronary arteries is not understood but may involve several

factors such as structural (vascular remodeling) and functional (endothelial dysfunction) changes. For example, vasodilator response of the left coronary artery could be abnormal in patients with left ventricular hypertrophy because the state of the artery at rest is "more dilated" than usual as a result of increased shear stress due to higher blood flow; such changes would lead to enhanced release of endothelium-derived relaxing factor, and, thus, to vascular smooth muscle relaxation with increased medial circumference. Therefore, the release of endothelium-derived relaxing factor is chronically stimulated by the increase in left ventricular mass (30); thus, signal transduction mechanisms relating left ventricular mass to left coronary artery dimension are intact but perhaps maximally stimulated. In this regard, a reduced coronary vasodilator capacity has been reported after administration of sublingual nitroglycerin in patients with left ventricular pressure overload hypertrophy due to aortic stenosis (31). In contrast, the increase in left ventricular mass may cause or be associated with a defect in the signal transduction mechanisms that relate blood flow to vessel caliber. In this case, the defect in signal transduction mechanisms would inhibit the left coronary artery from responding appropriately to an increase in left ventricular mass.

Although increased coronary blood flow has been postulated to be the major growth stimulus, enlargement of the coronary arteries may be related to other factors such as perfusion pressure, endothelium-derived relaxing factor (32–34), circulating neurohormones and local growth factors (34,35).

As long as coronary artery enlargement is "adequately" matched to left ventricular muscle mass, it allows mean flow velocity and shear stress to be kept normal despite the increase in absolute coronary blood flow (13,36,37). This mechanism depends largely on the capacity of the endothelium to sense shear stress and, thus, to release the endothelium-derived relaxing factor (38,39). However, an impaired coronary vasodilator response to intracoronary nitroglycerin has been reported in patients with dilated cardiomyopathy (40) and aortic valve disease (31).

In agreement with previous reports from our group (4), different patterns of changes in coronary artery size have been observed for the right and left coronary artery. Whereas the left coronary artery seems to follow changes in left ventricular mass, the right coronary artery does not. For instance, cross-sectional area of the proximal right coronary artery was directly correlated with mean pulmonary artery pressure (Fig. 4), suggesting that right coronary artery dimensions are influenced by the extent of right ventricular pressure overload and, hence, right ventricular muscle mass.

Limitations of the study. Other determinants of coronary artery size must also be addressed, such as age, gender, body surface area and coronary basal vasomotor tone (11,41). In the present study, age, gender and body surface area were similar in patients with hypertrophic or dilated cardiomyopathy and control subjects. Heart rate was similar in all three groups, suggesting that "overall" autonomic nervous activity was sim-

ilar. Thus, it can be assumed that sympathetic coronary vasomotor tone was comparable in the control subjects and the patients with hypertrophic or dilated cardiomyopathy.

Conclusions. Coronary artery size is increased in patients with hypertrophic or dilated cardiomyopathy to an extent similar to that in patients with secondary left ventricular hypertrophy. The enlargement of the proximal left coronary artery correlates directly with the increase in left ventricular muscle mass, but coronary artery size remains inappropriate with regard to the degree of left ventricular hypertrophy. Thus, coronary arteries in patients with severe left ventricular hypertrophy are relatively too small for the degree of hypertrophy and may contribute to subendocardial hypoperfusion in situations of high demand, causing angina pectoris, increased ventricular ectopic activity and sudden cardiac death. The main determinant of size seems to be left ventricular hypertrophy for the left coronary artery and mean pulmonary artery pressure for the right coronary artery. Thus, the stimulus for growth of the coronary arteries seems to be similar in primary and secondary left ventricular hypertrophy and probably is directly related to muscle mass and flow.

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