Int J Cardiovasc Imaging (2007) 23:671–677
DOI 10.1007/s10554-006-9186-4

ORIGINAL PAPER

Tortuosity of coronary arteries: an indicator for impaired left ventricular relaxation?

Okan Turgut · Ahmet Yilmaz · Kenan Yalta · Birhan M. Yilmaz · Ali Ozyol · Omer Kendirlioglu · Filiz Karadas · Izzet Tandogan

Received: 3 September 2006 / Accepted: 20 October 2006 / Published online: 10 January 2007

Abstract
Objective To investigate the relationship between coronary tortuosity and impaired left ventricular relaxation.
Methods One hundred and four subjects who underwent coronary angiography were included in the study. Left anterior descending, left circumflex, and right coronary arteries were traced. Tortuosity was identified by the finding of ≥3 bends (defined as ≥45° change in vessel direction) along main trunk of at least one artery. Study population were divided into tortuosity ($n = 54$) and no tortuosity ($n = 50$) groups. Subjects were all submitted to pulsed-wave Doppler and two-dimensional echocardiographic examination to assess left ventricular functions.
Results For subjects with tortuosity, early transmitral inflow (E) velocity was lower, late transmitral inflow (A) velocity was higher, E/A ratio was smaller compared with subjects without tortuosity ($P < 0.001$). Subjects with tortuosity had longer deceleration time of E velocity (DT) and isovolumic relaxation time (IVRT) than did subjects without tortuosity ($P < 0.001$). End-diastolic interventricular septal and left ventricular posterior wall thicknesses were greater in subjects with tortuosity than those without tortuosity ($P = 0.01$ and $P = 0.005$). There was an inverse correlation between total number of arteries with tortuosity and E/A ratio ($r = –0.750$, $P < 0.001$). Total number of arteries with tortuosity displayed correlations with DT ($r = 0.723$, $P < 0.001$) and IVRT ($r = 0.703$, $P < 0.001$).
Conclusions This study depicts that coronary tortuosity is associated with impaired left ventricular relaxation.Thus, coronary tortuosity might be an indicator of impaired left ventricular relaxation.

Keywords Angiography · Coronary tortuosity · Diastolic dysfunction · Echocardiography

Abbreviations

A	Peak late mitral inflow
BMI	Body mass index
CI	Confidence interval
E	Peak early mitral inflow
DT	Deceleration time of the E velocity
IVRT	Isovolumic relaxation time
IVS	Interventricular septal wall thickness at end-diastole
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LVEF	Left ventricular ejection fraction
OR	Odds ratio

O. Turgut (✉) · A. Yilmaz · K. Yalta · B. M. Yilmaz · A. Ozyol · O. Kendirlioglu · F. Karadas · I. Tandogan
Department of Cardiology, Faculty of Medicine, Cumhuriyet University, Istasyon Caddesi Esen Sitesi, A-Blok No: 21, Sivas 58030, Turkey
e-mail: okanturgut@walla.com

PW Left ventricular posterior wall thickness at end-diastole

1 Introduction

Coronary angiography, despite current shortcomings, has been regarded as golden standard for the evaluation of coronary arteries. Tortuosity of coronary arteries is a common finding during angiography and its extent correlates well with aging [1]. Hemodynamic shearing forces involved in tortuous arteries may affect the formation and subsequent rupture of atherosclerotic plaques giving rise to acute coronary syndromes [2–4]. Echocardiography has likewise maintained its role as an indispensable diagnostic tool in the assessment of both systolic and diastolic functions of the left ventricle. Impaired left ventricular relaxation detected by echocardiography is a frequently encountered entity and apart from coronary artery disease, it is associated with advanced age [5–7], obesity [8, 9], hypertension [10, 11], diabetes mellitus [12, 13], and hypercholesterolemia [14]. Nevertheless, to our knowledge, consistent evidence is little about the link between coronary tortuosity and abnormal left ventricular relaxation. We therefore conducted a prospective study to investigate the possible relationship between tortuosity of coronary arteries and impaired left ventricular relaxation. An angiographic finding that could help predict those with a pattern of diastolic dysfunction might influence management.

2 Methods

2.1 Subjects

This study included 322 consecutive individuals (aged 27–79 years) who underwent coronary angiography in our department during a 3-month period. Clinical cardiologists determined the indication for angiography. Subjects were excluded if they had significant coronary artery disease (presence of at least one lesion causing ≥50% diameter stenosis), previous surgical/percutaneous coronary revascularization, unsatisfactory visualization of the coronary arteries, electronic cardiac pacemaker, atrial fibrillation, dilated heart disease, or significant valvular disease. The remaining 104 participants in this study were divided into two groups according to the presence of coronary tortuosity. Group 1 consisted of 54 individuals with tortuosity of coronary arteries, and group 2 consisted of 50 individuals without tortuosity of coronary arteries.

2.2 Definition of risk factors

In all subjects, a fasting blood sample was collected at the beginning of cardiac catheterization for detailed lipid analysis. Hypercholesterolemia was defined as a total plasma cholesterol level of ≥200 mg/dl or a low-density lipoprotein-cholesterol level of ≥130 mg/dl, or using cholesterol-lowering drugs at the time of the investigation. Hypertension was defined as systolic blood pressure of ≥140 mmHg, or diastolic blood pressure of ≥90 mmHg in at least two separate readings diagnosed as hypertension by a physician; or taking antihypertensive medication. Diabetes mellitus was diagnosed if the fasting plasma glucose level was ≥126 mg/dl on two separate occasions, or if the subject was being treated with insulin or oral antihyperglycemic agents. Smokers were defined as those who had been smoking regularly until admission. Body mass index (BMI) is defined as weight in kilograms divided by height in meters squared. Obesity was defined as a BMI of ≥30 kg/m^2.

2.3 Coronary angiography

Selective coronary angiography was performed with the standard technique using an Infinix-CC (Toshiba Corp., Tokyo, Japan) X-ray system. The left anterior descending coronary artery (LAD), the left circumflex coronary artery (LCX), and the right coronary artery were traced, and tortuosity was determined in right/left anterior oblique and anteroposterior views with various cranial and caudal angulations. Tortuosity was identified by the finding of ≥3 bends (defined as ≥45° change in vessel direction) along the main trunk of at

least one artery, present both in systole and in diastole [15] (Fig. 1).

2.4 Echocardiography

Resting transthoracic echocardiography was done using a Vivid 4 (GE/VingMed, Horten, Norway) ultrasound system, equipped with a multifrequency (1.5–3.6 MHz) phased-array transducer. One of two experienced operators blinded to all clinical and angiographic data perfomed echocardiographic examination, which comprised standard two-dimensional imaging and pulsed-wave Doppler evaluation of the mitral inflow [16, 17]. Images were acquired in left lateral recumbent position. Left ventricular ejection fraction (LVEF) was calculated offline with the use of area-length method. Interventricular septal wall thickness at end-diastole (IVS) and left ventricular posterior wall thickness at end-diastole (PW) were measured as well. All Doppler echocardiographic recordings were obtained during quiet breathing. Measurements were averaged over three sequential cardiac cycles for each Doppler parameter. From apical window, pulsed-wave Doppler sample volume was placed at the mitral leaflet tips. The mitral inflow velocity was traced and the following variables were derived: peak early (E) and late (A) transmitral inflow velocities, the ratio of early to late peak velocities (E/A), and deceleration time of the E velocity (DT). In order to treat the E/A ratio as a continuous variable, subjects with a restrictive pattern (E/A ≥ 2), or with suspected pseudonormalization (during phase 2 of the Valsalva maneuver; E/A < 1, or the E/A ratio decreased by $\geq 25\%$ [18]) were excluded from the study. Using pulsed-wave Doppler echocardiography, the cursor was positioned midway between the left ventricular outflow and the mitral inflow to record the isovolumic relaxation time (IVRT) (Fig. 2). Both inter- and intraobserver variations for echocardiographic measurements were $< 5\%$ in 20 randomly selected participants.

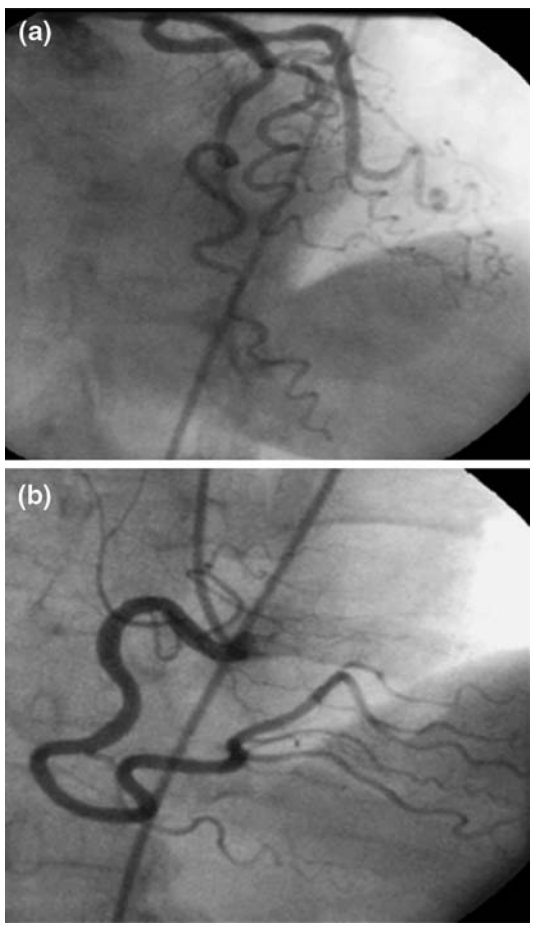

Fig. 1 Coronary angiograms showing tortuosity in anteroposterior view with cranial angulation (**a**) Left anterior descending and left circumflex coronary arteries (**b**) Right coronary artery

2.5 Statistical analysis

SPSS Version 10.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform all statistical calculations. Continuous variables were expressed as arithmetic mean ± standard deviation, and categorical variables as percentages. Comparisons of continuous variables between the two groups were carried out by Mann-Whitney *U* test. Categorical variables were compared by chi-square test. Spearman's coefficients were employed for correlation analysis. Multivariate logistic regression analysis was used to find out variables for tortuosity status. For multivariate regression, variables with a *P* value of < 0.1 in univariate analysis were selected. For all tests, a two-tailed *P* value of < 0.05 indicated statistical significance.

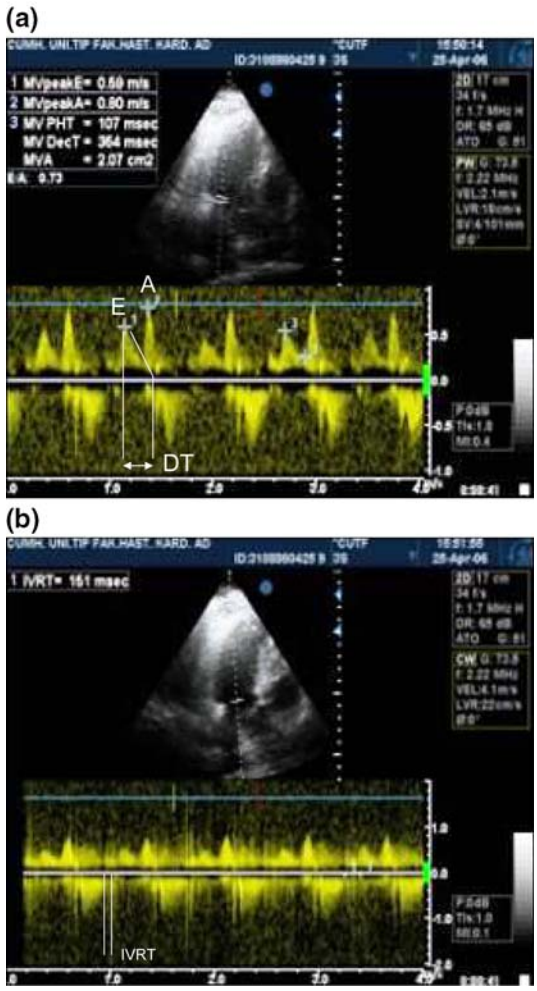

Fig. 2 Measurement of pulsed-wave Doppler echocardiographic parameters (**a**) Mitral inflow variables are shown. (**b**) Isovolumic relaxation time is shown

3 Results

Of 322 individuals who underwent coronary angiography, 218 were excluded: 6 subjects (2%) had angiograms with unsatisfactory visualization, 141 subjects (44%) had significant de novo coronary artery disease, 35 subjects (11%) had previous coronary revascularization, 3 subjects (1%) had electronic cardiac pacemaker, 10 subjects (3%) had atrial fibrillation, 10 subjects (3%) had dilated cardiomyopathy, 13 subjects (4%) had significant valvular disease. There were 69 (66%) men (age, 54 ± 11 years; range, 27–76 years) and 35 (34%) women (age, 55 ± 10 years; range, 35–79 years) in the study. Baseline clinical characteristics of subjects with and without tortuosity were similar (Table 1). The two groups were not significantly different in terms of age, and gender, as well as hypertension, diabetes mellitus, insignificant coronary artery disease, smoking, hypercholesterolemia, and obesity ($P > 0.05$ for all variables).

Although no significant difference was present between the groups concerning LVEF; for subjects with tortuosity, the E velocity was lower, the A velocity was higher, and thus the E/A ratio was smaller compared with subjects without tortuosity ($P < 0.001$). Subjects with tortuosity had significantly longer DT and IVRT than did subjects without tortuosity ($P < 0.001$). Furthermore, IVS and PW were both found to be greater in subjects with tortuosity compared with those without tortuosity ($P = 0.01$ and $P = 0.005$) (Table 2). Particularly, there was a strong inverse correlation between the total number of arteries with tortuosity and the E/A ratio ($r = –0.750$, $P < 0.001$). In addition, the total number of arteries with tortuosity displayed significant correlations with DT ($r = 0.723$, $P < 0.001$) and IVRT ($r = 0.703$, $P < 0.001$).

Multivariate logistic regression analysis was used to ascertain variables involved in tortuosity status. Following variables were used: Age, male gender, hypertension, diabetes mellitus, insignificant coronary artery disease, smoking, hypercholesterolemia, obesity, the E/A ratio, DT, IVRT, IVS, PW and LVEF. The E/A ratio (odds ratio [OR] = 0.005; 95% confidence interval [CI], 0.001–0.906; $P = 0.046$) and IVRT (OR = 1.362; 95% CI, 1.057–1755; $P = 0.017$) were the only variables associated with tortuosity status (Table 3).

4 Discussion

The key finding of our study is that impaired left ventricular relaxation is more prominent in individuals with tortuosity of coronary arteries than in individuals without tortuosity of coronary arteries. Of note, the total number of coronary arteries with tortuosity is shown to be correlated with the changes in Doppler echocardiographic indices (the decrease of the E/A ratio, and the increase of DT and IVRT) reflecting impaired left ventricular relaxation.

Table 1 Baseline clinical characteristics of subjects with and without tortuosity

Characteristic	Tortuosity (n = 54)	No tortuosity (n = 50)	P value
Age (years)*	56 ± 8	53 ± 13	0.321
Gender (male)	36 (67%)	33 (66%)	0.999
Hypertension	38 (70%)	28 (56%)	0.283
Diabetes mellitus	11 (20%)	8 (16%)	0.763
Insignificant coronary artery disease †	27 (50%)	24 (48%)	0.999
Smoking	10 (18%)	17 (34%)	0.228
Hypercholesterolemia	24 (44%)	26 (52%)	0.392
Obesity	14 (26%)	19 (38%)	0.249

* Data are presented as arithmetic mean ± standard deviation

† Presence of at least one lesion causing < 50% diameter stenosis

Table 2 Echocardiographic parameters of subjects with and without tortuosity*

Parameter	Tortuosity (n = 54)	No tortuosity (n = 50)	P value
E velocity (cm/s)	67 ± 18	90 ± 16	< 0.001
A velocity (cm/s)	89 ± 19	68 ± 15	< 0.001
E/A ratio	0.76 ± 0.22	1.3 ± 0.18	< 0.001
DT (ms)	303 ± 60	206 ± 13	< 0.001
IVRT (ms)	150 ± 25	99 ± 11	< 0.001
IVS (mm)	11.6 ± 1.5	10.7 ± 1.5	0.01
PW (mm)	10.9 ± 1.1	9.8 ± 1.6	0.005
LVEF (%)	61 ± 6	62 ± 7	0.575

* Data are presented as arithmetic mean ± standard deviation. A, peak late mitral inflow; E, peak early mitral inflow; DT, deceleration time of the E velocity; IVRT, isovolumic relaxation time; IVS, interventricular septal wall thickness at end-diastole; LVEF, left ventricular ejection fraction; PW, left ventricular posterior wall thickness at end-diastole

There are some determinants for tortuosity of coronary arteries. Differences in tortuosity have been observed between systole and diastole, and between circumferentially and longitudinally oriented coronary arteries. It has been demonstrated that tortuosity increases during systole and is more pronounced in circumferentially (LCX) than in longitudinally (LAD) running arteries in hypertensive patients [19].

Similarly, changes in left ventricular geometry due to chronic left ventricular pressure and volume overload influence tortuosity of coronary arteries, so that concentric hypertrophy seems to cause an increase in tortuosity [19, 20]. One probable interpretation includes here the possibility that associated abnormal left ventricular relaxation might be linked to coronary tortuosity. This is also concordant with our finding that both IVS and PW were greater among subjects with tortuosity than among those without tortuosity. Hypertension may lead to both tortuosity and impaired diastolic left ventricular function. It has been documented that impaired left ventricular relaxation detected by echocardiography is associated with hypertension [10, 11]. Hypertrophy basically induces an increase in tortuosity probably due to angiogenetic factors, which may be mediated through blood flow, wall stress, or growth factors [21, 22].

Age per se is also a determinant for tortuosity of coronary arteries. However, previous studies have pointed out that the correlation between tortuosity and age was weak although significant. The reason for this increase in tortuosity with age is not clear but may be dependent on left ventricular hypertrophy and concomitant impaired relaxation, which have been found to be more common in elderly people. In this context, tortuosity is the result of structural and operational alteration of the heart and may represent an adaptive mechanism to allow the heart to change its size and function.

Besides, a unique feature of coronary vasculature that differs from all other arterial sites is the repetitive flexion during each cardiac contraction. Such cyclic flexion producing shear stresses, especially at tortuous sites, may bring about tissue fatigue and endothelial injury, allowing adhesions of platelet thrombi and deposition of cholesterol particles that can contribute to the initiation and progression of atheromatous plaques [23].

4.1 Limitations of our study

Due to strict inclusion criteria for minimizing effects of confounding factors on outcomes we had to include only a limited number of subjects in stable conditions, presumably not representative of the status of more general populations referred for clinical management. Hence, the link between impaired left ventricular relaxation

Table 3 Multivariate logistic regression analysis of selected variables for tortuosity status

Variable	Wald chi-square	OR	95% CI	*P* value
Age	1.858	0.903	0.781–1.046	0.173
Male gender	0.082	2.522	0.005–14.161	0.774
Hypertension	2.501	55.715	0.370–83.137	0.116
Diabetes mellitus	2.175	42.010	0.911–184.640	0.147
Insignificant coronary artery disease	0.009	1.139	0.072–17.888	0.926
Smoking	3.933	75.905	0.355–162.943	0.114
Hypercholesterolemia	2.469	0.007	0.001–3.586	0.119
Obesity	0.610	0.940	0.804–1.098	0.434
E/A ratio	5.612	0.005	0.001–0.906	0.046
DT	0.091	1.014	0.925–1.111	0.764
IVRT	5.687	1.362	1.057–1.755	0.017
IVS	0.004	1.139	0.020–4.544	0.950
PW	2.432	24.017	0.036–162.280	0.140
LVEF	3.987	0.558	0.344–1.904	0.088

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 2

and tortuosity of coronary arteries observed in our study was in part dependent on the close relationship in this group of participants. Due to proven relationship between hypertension and vessel tortuosity it is also important to mention that a numeric trend was present (70% vs. 56%) which did not attain significance most probably because of small number of subjects studied. A relatively substantial proportion of individuals were a priori excluded for technical limitations of Doppler echocardiography. The aim of the study was to analyze the potential role of coronary tortuosity as an indirect marker of impaired left ventricular relaxation, and this information appears particularly useful for those without reliable Doppler information. Thus, this unavoidable drawback should be acknowledged in the clinical application of our data.

Dependence of left ventricular relaxation on loading conditions was not taken into account. Moreover, indices of left ventricular relaxation were derived from Doppler echocardiography for practical reasons and no invasive pressure monitoring was performed, whereas cardiac catheterization remains the most invaluable technique for direct assessment of diastolic function. However, Doppler parameters have been extensively validated to correlate with hemodynamic findings [24].

Flow pattern, length and shear stress of coronary arteries were not measured. Coronary flow is another factor which may have an impact on tortuosity. An increase in flow, as is seen in left ventricular hypertrophy, might stimulate not only growth in caliber but also in length, as with collateral growth. Tortuosity of coronary arteries may also be influenced by the shape of the heart, that is, by the geodesic curves of coronary arteries. This effect, on the other hand, appears to be small because these curves are relatively larger compared with tortuosity of the vessel. It should be borne in mind that this is an observational study with a real risk of resultant statistical associations occurring that are due to probability alone.

Consequently, these results indicate that, tortuosity of coronary arteries is associated with impaired left ventricular relaxation, suggesting the presence of a tentative common pathophysiological pathway leading to reciprocal interaction. Then, coronary tortuosity might conceivably possess an adjunctive merit in estimating left ventricular filling pattern and have promising implications for discerning persons who require meticulous follow-up. We think that it may be an interesting tool for future cardiovascular imaging research and further studies are needed to confirm a causal relation.

References

1. Hutchins GM, Bulkley BH, Miner MM, Boitnott JK (1977) Correlation of age and heart weight with tortuosity and caliber of normal human coronary arteries. Am Heart J 94:196–202
2. Gertz SD, Roberts WC (1990) Hemodynamic shear force in rupture of coronary arterial atherosclerotic plaques. Am J Cardiol 66:1368–1372
3. Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT (1993) Distribution of circumferential stress in

ruptured and stable atherosclerotic lesions. A structural analysis with histopathological correlation. Circulation 87:1179–1187
4. Tengiz I, Aliyev E, Ercan E (2005) An alternative percutaneous interventional approach for post-anastomatic left anterior descending artery stenosis in patients with markedly tortuous LIMA graft. Int J Cardiovasc Imaging 21:491–494
5. Cacciapuoti F, D'Avino M, Lama D, Bianchi U, Perrone N, Varricchio M (1992) Progressive impairment of left ventricular diastolic filling with advancing age: a Doppler echocardiographic study. J Am Geriatr Soc 40:245–250
6. Yamada H, Oki T, Mishiro Y et al (1999) Effect of aging on diastolic left ventricular myocardial velocities measured by pulsed tissue Doppler imaging in healthy subjects. J Am Soc Echocardiogr 12:574–581
7. Tokushima T, Reid CL, Gardin JM (2001) Left ventricular diastolic function in the elderly. Am J Geriatr Cardiol 10:20–29
8. Stoddard MF, Tseuda K, Thomas M, Dillon S, Kupersmith J (1992) The influence of obesity on left ventricular filling and systolic function. Am Heart J 124:694–699
9. Berkalp B, Cesur V, Corapcioglu D, Erol C, Baskal N (1995) Obesity and left ventricular diastolic dysfunction. Int J Cardiol 52:23–26
10. Chang KC, Tseng YZ, Kuo TS, Chen HI (1994) Impaired left ventricular relaxation and arterial stiffness in patients with essential hypertension. Clin Sci (Lond) 87:641–647
11. Musiari L, Ceriati R, Taliani U, Montesi M, Novarini A (1999) Early abnormalities in left ventricular diastolic function of sodium-sensitive hypertensive patients. J Hum Hypertens 13:711–716
12. Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA (2001) Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am J Cardiol 87:320–323
13. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE (2004) Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. Am J Cardiol 93:870–875
14. Paolisso G, Cacciapuoti F, Lama D, Galzarano D, Varricchio M, D'Onofrio F (1992) Impaired left ventricular relaxation and hyperinsulinemia in patients with primary hypercholesterolemia. Atherosclerosis 96:65–70
15. Zaacks SM, Allen JE, Calvin JE et al (1998) Value of the American College of Cardiology/American Heart Association stenosis morphology classification for coronary interventions in the late 1990s. Am J Cardiol 82:43–49
16. Schiller NB, Shah PM, Crawford M et al (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 2:358–367
17. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL (1996) A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. J Am Coll Cardiol 27:1753–1760
18. Dumesnil JG, Gaudreault G, Honos GN, Kingma JG Jr (1991) Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by Doppler echocardiography in patients with coronary artery disease or systemic hypertension. Am J Cardiol 68:515–519
19. Jakob M, Spasojevic D, Krogmann ON, Wiher H, Hug R, Hess OM (1996) Tortuosity of coronary arteries in chronic pressure and volume overload. Cathet Cardiovasc Diagn 38:25–31
20. Dagianti A, Rosanio S, Luongo R, Dagianti A, Fedele F (1993) Coronary morphometry in essential arterial hypertension. Cardiologia 38:497–502
21. Komuro I, Katoh Y, Kaida T et al (1991) Mechanical loading stimulates cell hypertrophy and specific gene expression in cultured rat cardiac myocytes. Possible role of protein kinase C activation. J Biol Chem 266:1265–1268
22. Davies PF, Tripathi SC (1993) Mechanical stress mechanisms and the cell. An endothelial paradigm. Circ Res 72:239–245
23. Stein PD, Hamid MS, Shivkumar K, Davis TP, Khaja F, Henry JW (1994) Effects of cyclic flexion of coronary arteries on progression of atherosclerosis. Am J Cardiol 73:431–437
24. Appleton CP, Hatle LK, Popp RL (1988) Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 12:426–440