Echocardiographic Evaluation and Clinical Implications of Aortic Stiffness and Coronary Flow Reserve and Their Relationship

Address for correspondence:
Attila Nemes, MD, PhD, FESC
Second Department of Medicine and Cardiology Centre
Albert Szent-Györgyi Medical and Pharmaceutical Centre
University of Szeged
P.O. Box 427 H-6720 Szeged,
Korányi fasor 6, Hungary
nemes@in2nd.szote.u-szeged.hu

Attila Nemes, MD, PhD, FESC,* Marcel L. Geleijnse, MD, PhD,† Tamás Forster, MD, PhD, DSC, FESC,* Osama I. I. Soliman, MD,† Folkert J. Ten Cate, MD, PhD, FESC, FACC,† Miklós Csanády, MD, PhD, DSC, FESC, FACC*

*Second Department of Medicine and Cardiology Center, Medical Faculty, Albert Szent-Györgyi Medical and Pharmaceutical Center, University of Szeged, Szeged, Hungary; †Department of Cardiology, Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands

ABSTRACT

The normal human aorta is not a stiff tube, but is characterized by elastic properties with a buffering Windkessel function. Aortic stiffening may cause an increase in aortic pulse pressure, left ventricular (LV) load, and ultimately left ventricular hypertrophy. This, together with the decreased diastolic transmyocardial pressure gradient, interacts with coronary flow and flow reserve. In recent studies, significant correlations between coronary flow reserve and aortic stiffness have been demonstrated in different patient populations. The aim of this review is to describe the current echocardiographic modalities to measure aortic stiffness and coronary flow reserve, and to overview knowledge about the relationship between aortic stiffness and coronary flow reserve.

Key words: aortic stiffness, coronary flow reserve, echocardiography

Introduction

The normal human aorta is not a stiff tube, but is characterized by elastic properties. During systole, the left ventricle ejects a stroke volume into the arterial system. A half of this stroke volume is directly forwarded to the peripheral circulation, but because of peripheral resistance and elastic extension of the aortic wall, the other half of the stroke volume is stored in the aorta.[1] During diastole, when the aortic valve is closed and there is no further blood ejection, aortic pressure falls, the aorta recoils slowly, and the stored volume is pressed into the peripheral circulation. This volume buffering function is known as the Windkessel function.[2] Normally, LV ejection causes a pressure pulse with a relatively slow pulse wave velocity (PWV). When this wave is reflected by the peripheral circulation, it returns to the ascending aorta during early diastole inducing the dicrotic wave.[3] This second increase in pressure is normally dampened by the Windkessel function.

Arterial Stiffness

The elastic properties of the aorta incorporate both the property of dilating by increasing pressure in systole, and the property of recoiling slowly to its initial shape when blood pressure falls in diastole. Aortic stiffness describes the elastic resistance that the aorta sets against its distension. The inverse of stiffness is compliance, which describes the ease of systolic aortic expansion. In humans, physiologically increased aortic stiffness is seen in the more distal aortic parts[4] in men[5] and in the elderly.[1]

Aortic stiffness also increases when the intraluminal pressure is high (a complex reciprocal influence exists between aortic stiffness and pressure)[6] or when the arteries stiffen due to pathophysiologic conditions such as atherosclerosis, diabetes, hypertension, renal failure, and connective tissue diseases.[1] In these conditions the aortic wall is characterized by fibrosis, medial smooth muscle cell necrosis, breaks in elastin fibers, calcifications, or diffusion of macromolecules into the arterial wall. Owing to these alterations, the aorta stiffens and the Windkessel function attenuates. As a result, the amplitude of the outgoing pressure pulse and the PWV is increased, causing reflected pressure wave components to return more early (in late systole) to the aortic root. There, they boost pressure levels in late systole whereas ejection is still infolding, thereby increasing the LV load.[6]

Evaluation of Aortic Stiffness

To evaluate aortic stiffness, 2 important variables should be noted: the change in volume due to blood injection in the aorta, and the pressure change caused by this volume change.[1] To noninvasively quantify aortic stiffness measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP), changes in aortic diameters, that is, systolic diameter (SD) and diastolic diameter (DD), are necessary. Aortic diameters can be measured noninvasively with echocardiography, computed tomography, and magnetic resonance imaging. During transthoracic echocardiography (TTE), SD and DD can be recorded in the motion

Clin. Cardiol. 31, 7, 304–309 (2008)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20252

Received: April 18, 2007
Accepted with revision: July 23, 2007

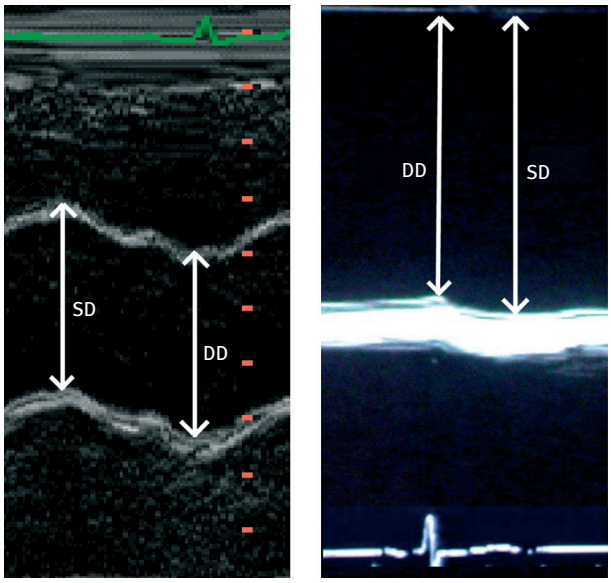

Figure 1: With TTE, SD and DD can be recorded in M-mode at a level of 3 cm above the aortic valve from a parasternal long-axis view. The SD and DD can be measured at the time of maximum aortic anterior motion and at the peak of the QRS complex, respectively (Figure 1A). With TEE, diameters should be measured at each level of descending aorta with M-mode (Figure 1B).

mode (M-mode) at a level of 3–4 cm above the aortic valve from a transthoracic parasternal long-axis view, at the time of maximum aortic anterior motion, and at the peak of the QRS complex, respectively (Figure 1A). With transoesophageal echocardiography, diameters should be measured at each level of the descending aorta with M-mode (Figure 1B). To assess aortic elasticity, several parameters (i.e., indices or moduli) can be calculated by using aortic diameter and blood pressure data. For instance:

- Aortic diameter change (mm) = SD−DD;
- Aortic strain = (SD−DD)/DD;
- Elastic modulus E(p) = (SBP−DBP) / strain;
- Young's circumferential static elastic modulus E(s) = E(p) ∗ DD / 2h, where 'h' means diastolic intima-media thickness;
- Aortic stiffness index β = ln (SBP/DBP) / strain, where 'ln' means natural logarithm;
- and Aortic distensibility = (2 x strain) / (SBP−DBP).

Stefanadis et al. demonstrated that the noninvasively evaluated aortic stiffness index β is comparable with invasive methods with a high degree of accuracy.[7] It should be noted that measurement of changes in the aortic circumference is theoretically more accurate than the measurement of changes in the aortic diameter due to the noncircular shape of the aorta (Figure 2). One disadvantage of this evaluation of aortic stiffness is that regionality is not taken into consideration. Drozdz et al. demonstrated that 3-Dimensional (3-D) transesophageal echocardiography (TEE) has a strong potential for regional aortic stiffness measurements using horizontal cross-sectional imaging of the vessel.[8] Recently, we demonstrated the usefulness of real-time, 3-D, TTE for regional assessment of aortic stiffness.[9] As seen in figure 3, the cut planes from the 3-D datasets that visualized the aorta en-face could be easily reconstructed. The reconstructed images allow segmental evaluation of aortic cross-sections at different levels. Regional aortic elastic properties can be calculated using blood pressure data, and regional aortic SD and DD. It should be noticed that all noninvasive cardiac imaging modalities, including echocardiography, magnetic resonance imaging, and computed tomography, are able to create cross-sectional images at different levels of the aorta. However, at the moment there is no information available as to which imaging modality is preferred, and what additional information that the regional stiffness offers.

Evaluation of Pulse Wave Velocity

Another noninvasive opportunity to characterize aortic stiffness is by measuring PWV. Different echocardiographic and tonometric methods can be used for PWV measurement. During the echocardiographic evaluation, 2 transducers are necessary to record the arterial wave simultaneously at the common carotid and femoral arteries. The PWV can be calculated as the travel distance between the 2 transducers, measured on the body surface, divided by the transit time, and determined manually by the foot-to-foot velocity method (Figure 4).

Coronary Flow Reserve

In a normal situation, coronary blood flow can increase approximately 4- to 6-fold to meet increasing myocardial metabolic demands. This effect is mediated by vasodilation of the arteriolar bed, which reduces vascular resistance, thereby increasing coronary flow. Coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands, and can be expressed by the difference between the hyperemic flow and the resting flow curves. In 1974, Gould and Lipscomb proposed the relationship between the anatomic condition and the behavior of coronary hyperemic flow, whereby an inverse curvilinear relationship exists between the narrowing of the lumen of the coronary artery and hyperemic capacity, up to a complete annulment or absence of CFR for stenosis >90%.[10] Coronary flow reserve is affected by micro- and macrovascular resistance, extravascular compressive forces (pathological LV hypertrophy), hypertension, metabolic factors (i.e.,

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20252

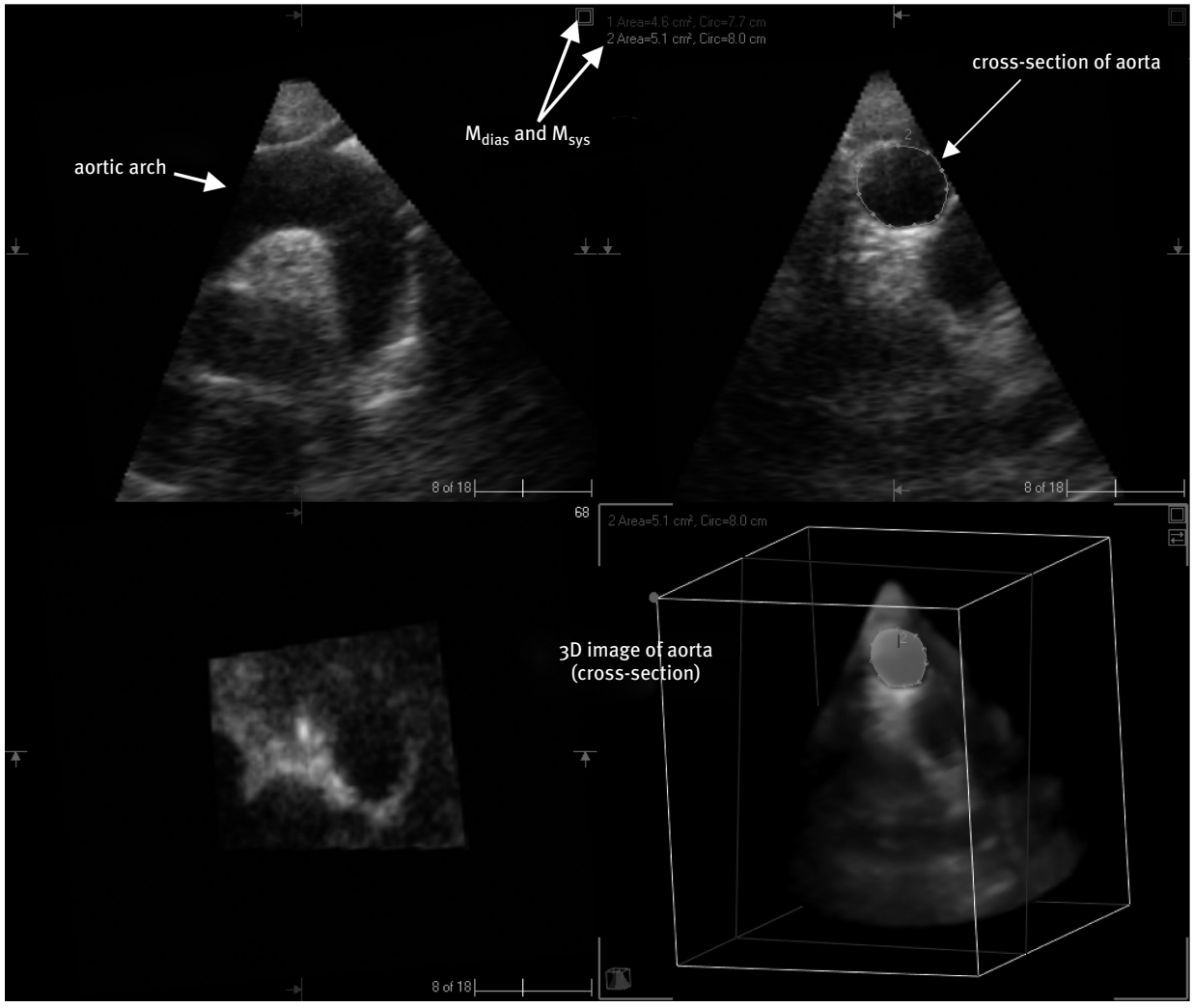

Figure 2: Real-time, 3-D echocardiography allows the exact measurment of shape and surface changes during a heart cycle at each level of the aorta. *Abbreviations*: M_{dias} = diastolic measurement of aortic surface in cm², M_{sys} = systolic measurement of aortic surface in cm².

diabetes mellitus, hypercholesterolaemia), hyperviscosity, smoking, autonomic neuropathy, insulin resistance, etc.

Echocardiographic Evaluation of Coronary Flow Reserve

Several echocardiographic methods are suitable for the evaluation of CFR, including contrast echocardiography[11] and direct Doppler measurement during transthoracic[12] or transesophageal measurements.[12,13] The original protocol of transesophageal Doppler CFR measurement in the left anterior descending (LAD) coronary artery was described by Iliceto et al.[13] After visualization of the aortic root and proximal portion of the LAD coronary artery, coronary blood flow velocities can be recorded by pulse-wave Doppler. Phasic coronary flow velocity patterns can be recorded under resting conditions and during hyperemia. As vasodilator agents, adenosine (infusion rate 0.14 mg/kg per min over 5 min)[14] and dipyridamole (infusion rate 0.56 mg/kg per min over 4 min[13] or 0.84 mg/kg per min over 10 min)[15] can be used. The CFR is estimated as the ratio of hyperaemic to basal peak diastolic coronary flow velocity. The independent prognostic value of pulse-wave Doppler-derived CFR during dipyridamole stress echocardiography has been demonstrated in patients with known or suspected coronary artery disease (CAD)[16] dilated cardiomyopathy,[17] and after heart transplantation.[18] However, owing to its semiinvasiveness (probe intubation), stress transoesophageal echocardiography-derived CFR measurement did not become popular among cardiologists. Although dipyridamole stress TTE can assess LV

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20252

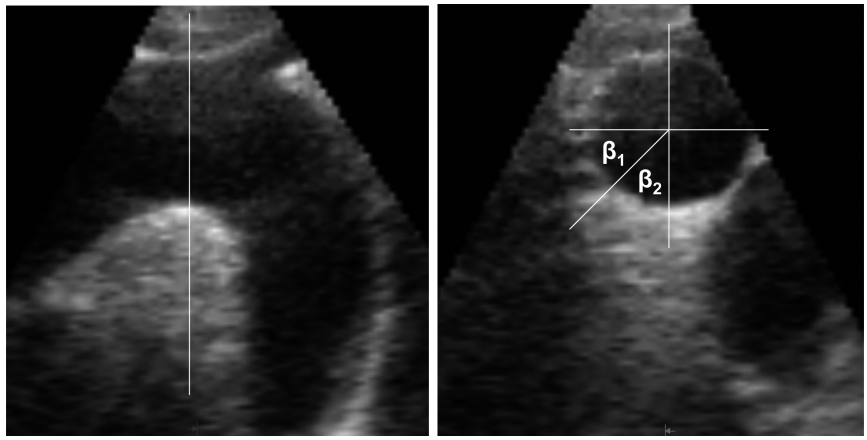

Figure 3: Real-time, 3-D echocardiography allows the evaluation of regionality of aortic stiffness.

wall motion and CFR, its value is limited because of difficult visualization of the proximal part of the LAD coronary artery.[15]

Real-time myocardial contrast echocardiography also allows the evaluation of myocardial flow reserve.[11] A contrast agent is continuously infused for 4 min to allow for steady blood concentration of the microbubbles. Then transient bursts with a highmechanical index (1.8) (flash imaging) is given to allow for microbubbles destruction within the LV myocardium. After these flashes are applied, contrast replenishment within the LV myocardium is studied. The replenishment slope is correlated with myocardial flow reserve. Stress images should be recorded after 8 min of adenosine infusion at a rate of 140 μg/kg/min. Myocardial flow reserve can be calculated by dividing the hyperemic and resting values.

Clinical Implications of Aortic Stiffness

Aortic stiffening leads to faster PWV, and thus an earlier pulse wave reflection, causing an increase in central SBP and a decrease in DBP with an increase in pulse pressure.[1] An increased SBP may increase the LV afterload with an increase in myocardial oxygen demand, LV hypertrophy, and fibrosis, and eventually a reduction in LV ejection fraction. Myocardial perfusion depends on the diastolic pressure gradient from epicardium to endocardium, and the duration of diastole. A decrease in DBP can compromise myocardial perfusion resulting in subendocardial ischemia. Moreover, a raised pulse pressure may induce arterial remodeling with an increase in wall thickness and plaque development. Stiffer arteries may contribute to ulceration and rupture of atherosclerotic plaques when inhomogeneity in stiffness in and around the plaque is present (increased shear stress).

In patients with moderate CAD, large artery stiffness is a major determinant of the myocardial ischemic threshold.[19] In addition, aortic PWV predicts cardiovascular events in patients with hypertension,[20] diabetes,[21] end-stage renal disease,[22] in hospitalized[23] or well-functioning elderly,[24] and in the general population.[25,26]

Relationship Between Aortic Stiffness and Coronary Flow Reserve

As described earlier, aortic stiffening may cause an increase in aortic pulse pressure, LV load, and ultimately, LV hypertrophy. This LV hypertrophy, together with the decreased diastolic transmyocardial pressure gradient caused by the decrease in DBP, interacts with CFR. Besides the aorto-coronary hemodynamic relationship, aortic stiffness may be a marker of a more generalized vascular disease or coexists with microvascular disease.[1]

The hypothesis that coronary flow may be influenced by aortic mechanical properties was introduced by Bouvrain and Levy,[27] and was confirmed by experimental studies.[28–30] Later, significant correlations between CFR and aortic stiffness assessed by PWV, were described in patients with hypertension[31] and CAD.[32,33] Aortic stiffness has been described to reduce the improvement in hyperemic coronary blood flow after a successful percutaneous coronary intervention.[33] We extensively investigated the usefulness of vasodilator stress TEE in the simultaneous evaluation of CFR and aortic elastic properties, estimated from cyclic changes in aortic diameter and blood pressure data.[12,34–39] We described reduced CFR and increased E(p) and E(s) (indices of aortic stiffness) in patients with LAD CAD as compared with patients with normal epicardial coronary arteries.[12] In patients with nonsignificant CAD, these values were intermediate between patients with LAD CAD and those with normal epicardial coronary arteries. In addition to these findings in patients with CAD, we demonstrated alterations in these 2 functional parameters in patients without CAD, but with hypertension,[36] aortic valve stenosis,[35]

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20252

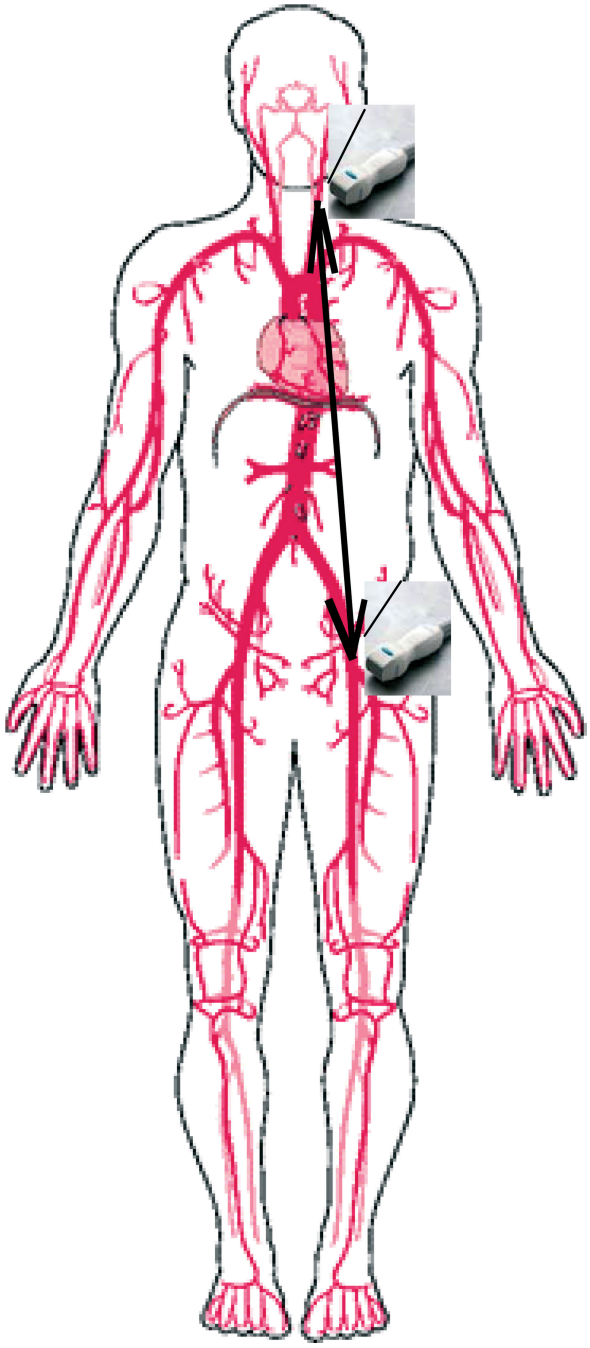

Figure 4: Evaluation of PWV. Two transducers are necessary to record the arterial wave simultaneously at the common carotid and femoral arteries. The PWV can be calculated as a travel distance between the 2 transducers, measured on the body surface, divided by the transit time, and determined manually by the foot-to-foot velocity method.

type-2 diabetes,[37] and hypercholesterolemia,[38] with significant correlations between the parameters. These studies confirm the relationship between the parameters of aortic stiffness and CFR.

Future research is warranted to provide more robust information on direct evaluation of aortic stiffness and CFR. Also, it should be investigated whether combining CFR with aortic elastic properties provides better prognostic information in specific subsets of patients.

References

1. Bader H: Importance of the gerontology of elastic arteries in the development of essential hypertension. *Clin Physiol Biochem* 1983;1:36–56
2. Belz GG: Elastic properties and Windkessel function of the human aorta. *Cardiovasc Drugs Ther* 1995;9:73–83
3. O'Rourke M: Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. *Hypertension* 1990;15:339–547
4. Mohiaddin RH, Underwood SR, Bogren HG, Firmin DN, Klipstein RH, et al.: Regional aortic compliance studied by magnetic resonance imaging: the effects of age, training, and coronary artery disease. *Br Heart J* 1989;62:90–96
5. Laogun AA, Gosling RG: In vivo arterial compliance in man. *Clin Phys Physiol Meas* 1982;3:201–212
6. Pasipoularides A: Complementarity and competitiveness of the intrinsic and extrinsic components of the total ventricular load: demonstration after valve replacement in aortic stenosis. *Am Heart J* 2007;153:4–6
7. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P: Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J* 1990;11:990–996
8. Drozdz J, Krzeminska-Pakuola M, Lipiec P, Orczykowski M, Chrzanowski O, et al.: Regional aortic function is correlated with intima-media thickness-insights from three-dimensional echocardiography. *J Am Soc Echocardiogr* 2005;18:789–794
9. Nemes A, Geleijnse ML, Soliman OI, Anwar AM, Vletter WB, et al.: Real-time three-dimensional echocardiography for regional evaluation of aortic stiffness. *Eur J Echocardiogr* 2007;8:161–162
10. Gould KL, Lipscomb K: Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 1974;34:48–55
11. Vogel R, Indermuhle A, Reinhardt J, Meier P, Siegrist PT, et al.: The quantification of absolute myocardial perfusion in humans by contrast echocardiography: algorithm and validation. *J Am Coll Cardiol* 2005;45:754–762
12. Nemes A, Forster T, Gruber N, Csanady M: Coronary flow velocity reserve and indices describing aortic distensibility in patients after coronary angiography. *Int J Cardiol* 2004;96:29–33
13. Iliceto S, Marangelli V, Memmola C, Rizzon P: Transesophageal Doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilation. *Circulation* 1991;83:61–69
14. Kozakova M, Palombo C, Pratali L, Bigalli G, Marzilli M, et al.: Assessment of coronary reserve by transoesophageal Doppler echocardiography. Direct comparison between different modalities of dipyridamole and adenosine administration. *Eur Heart J* 1997;18:514–523
15. Rigo F, Gherardi S, Galderisi M, Cortigiani L: Coronary flow reserve evaluation in stress-echocardiography laboratory. *J Cardiovasc Med (Hagerstown)* 2006;7:472–479
16. Rigo F, Cortigiani L, Pasanisi E, Richieri M, Cutaia V, et al.: The additional prognostic value of coronary flow reserve on left anterior descending artery in patients with negative stress echo by wall motion criteria. A Transthoracic Vasodilator Stress Echocardiography Study. *Am Heart J* 2006;151:124–130

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20252

17. Rigo F, Gherardi S, Galderisi M, Pratali L, Cortigiani L, et al.: The prognostic impact of coronary flow-reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy. *Eur Heart J* 2006;27:1319–1323
18. Tona F, Caforio AL, Montisci R, Gambino A, Angelini A, et al.: Coronary flow velocity pattern and coronary flow reserve by contrast-enhanced transthoracic echocardiography predict long-term outcome in heart transplantation. *Circulation* 2006;114:I49–I55
19. Kingwell BA, Waddell TK, Medley TL, Cameron JD, Dart AM: Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. *J Am Coll Cardiol* 2002;40:773–779
20. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, et al.: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–1241
21. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, et al.: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;106:2085–2090
22. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, et al.: Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003;63:1852–1860
23. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME: Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol* 2001;21: 2046–2050
24. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, et al.: Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 2005;111:3384–3390
25. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, et al.: Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006;113:664–670
26. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, et al.: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006;113: 657–663
27. Bouvrain Y, Levy B: "Windkessel" and coronary debit. *Arch Mal Coeur Vaiss* 1981;74:635–639
28. Ohtsuka S, Kakihana M, Watanabe H, Sugishita Y: Chronically decreased aortic distensibility causes deterioration of coronary perfusion during increased left ventricular contraction. *J Am Coll Cardiol* 1994;24:1406–1414
29. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y: Decreased aortic compliance aggravates subendocardial ischaemia in dogs with stenosed coronary artery. *Cardiovasc Res* 1992;26:1212–1218
30. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y: Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol* 1993;21:1497–1506
31. Wang GH, Hu DY: Effect of pulse wave velocity on coronary flow reserve in patients with essential hypertension. *Zhonghua Yi Xue Za Zhi* 2005;85:54–57
32. Fukuda D, Yoshiyama M, Shimada K, Yamashita H, Ehara S, et al.: Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. *Heart* 2006;92:759–762
33. Leung MC, Meredith IT, Cameron JD: Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. *Am J Physiol Heart Circ Physiol* 2006;290:H624–H630
34. Nemes A, Forster T, Csanady M, Gruber N: Indices of aortic distensibility and coronary flow velocity reserve in patients with different grades of aortic atherosclerosis. *Int J Cardiovasc Imag* 2004;20:271–277
35. Nemes A, Forster T, Csanady M: Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. *J Heart Valve Dis* 2004;13:567–573
36. Nemes A, Forster T, Csanady M: Simultaneous evaluation of coronary flow velocity reserve and aortic distensibility indices in hypertension. *Heart Vessels* 2007;22:73–78
37. Nemes A, Forster T, Csanady M: Reduced aortic distensibility and coronary flow velocity reserve in diabetes mellitus patients with a negative coronary angiogram. *Can J Cardiol* 2007;23:445–450
38. Nemes A, Forster T, Csanady M: Impaired coronary flow velocity reserve and aortic distensibility in patients with untreated hypercholesterolemia-an echocardiographic study. *Int J Cardiovasc Imag* 2007;23:15–23
39. Nemes A, Forster T, Csanady M: Relationship between coronary flow velocity reserve and aortic stiffness. *Am J Physiol Heart Circ Physiol* 2006;290:H1311

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20252