Vasoconstrictor component of atherothrombotic culprit lesions in ST-segment elevation myocardial infarction

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Objective: The vasoconstrictor component of atherothrombotic culprit lesions in ST-elevation myocardial infarction (STEMI) patients has not been fully investigated. This study was aimed at assessing the vasoconstrictor component of atherothrombotic culprit lesions in patients with STEMI receiving primary percutaneous coronary intervention (PCI).

Methods: A group of 100 patients with STEMI were enrolled prospectively. Baseline coronary angiography achieving normal antegrade flow was followed by 200 µg of intracoronary nitroglycerin (NTG) injection and repeat coronary angiography at the same projection view for culprit lesions was performed. End points were the changes in lesion length, reference vessel diameter, minimal lumen diameter, and diameter stenosis by quantitative coronary analysis before and after NTG injection.

Results: Reference vessel diameter (2.7 ± 0.5 mm vs. 2.9 ± 0.5 mm, p < 0.001) and minimal lumen diameter (0.9 ± 0.4 mm vs. 1.2 ± 0.5 mm, p < 0.001) increased after NTG injection, whereas lesion length (24.1 ± 7.4 mm vs. 23.4 ± 7.6 mm, p = 0.001) and diameter stenosis (66.6 ± 14.8% vs. 58.3 ± 16.1%, p < 0.001) decreased. The median percentage change of diameter stenosis was −4.0% (Interquartile range: −13.8% to −1.0%), which was used as the cut-off value to divide the cohort into NTG responder or nonresponder groups accordingly. Total stent length was significantly shorter in the responder group compared with the nonresponder group (27.4 ± 11.6 mm vs. 33.7 ± 16.8 mm, p = 0.042).

Conclusion: This study showed the presence of a vasoconstrictor component in atherothrombotic culprit lesions in STEMI patients receiving primary PCI. Vasodilating effort by NTG may decrease stent length used for culprit lesions.

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1. Introduction

Investigating vasoconstriction in culprit lesions is important to assess the true vessel size, and to reduce the risk of vasoconstrictor reactions during the procedure. Although pretreatment with an intracoronary administration of nitroglycerin (NTG) is recommended to unmask vasoconstriction in elective percutaneous coronary intervention (PCI), its effect on atherothrombotic culprit lesion in ST-segment elevation myocardial infarction (STEMI) patients has not been fully investigated [1].

In most STEMI cases, the main disease pathology is an atherothrombotic culprit lesion. The underlying plaque of the atherothrombotic culprit lesion is accompanied by endothelial disruption or denudation. Although these lesions may have a vasoconstrictor component, it is not easy to assess whether the occluded lesion with thrombus has a vasoconstrictor component. Therefore, assessing the true size of the vessel after relieving the vasoconstrictor component with flow improvement in culprit lesions of STEMI is a very important factor to determine the size and length of stent in primary PCI.

NTG is useful to avoid stent undersizing in PCI before assessing the reference vessel diameter [1]. Therefore, the objective of this study is to assess the vasoconstrictor component of atherothrombotic culprit lesions in STEMI patients receiving primary PCI before and after intracoronary NTG injection.

2. Materials and methods

2.1. Study population

This prospective multicenter registry study was carried out at three hospitals between September 2013 and December 2014. Consecutive patients presenting with STEMI undergoing primary PCI were included in this study. Fig. 1 shows the study flow chart. Patients with cardiogenic shock (blood pressure <90/60 mmHg), requiring mechanical support (intra-aortic balloon pump, extracorporeal membrane oxygenation, and pacemaker) and those known to have vasospastic angina were excluded from this study. Culprit lesions with thrombolysis in myocardial infarction (TIMI) <2 flow after revascularization with balloon angioplasty or thrombus aspiration were also excluded because the blood flow in those lesions did not fully recover. The culprit lesion was selected when the patient’s TIMI flow was restored to normal, followed by intracoronary NTG injection to the lesion to analyze the blood vessel response. The study protocol was approved by the Ethics Committee in Ulsan University Hospital and was in accordance with the Declaration of Helsinki.

2.2. Study procedures

All patients were prescribed a loading dose of aspirin 300 mg and clopidogrel 600 mg. To maintain an activated clotting time ≥250 seconds throughout the procedure 100 U/Kg of unfractionated heparin was injected intravenously. The use of glycoprotein IIb/IIIa inhibitors during the procedure was at the discretion of the operator. If initial antegrade flow in the culprit vessel was not TIMI 3, mechanical reperfusion to restore coronary flow was carried out in the form of balloon angioplasty or thrombus aspiration as determined by the operator to achieve TIMI 3 antegrade flow. Angiogram time interval was defined as the interval between the first and second angiogram for the culprit lesion after intracoronary administration of NTG. PCI was performed according to the standard techniques. Stent length and size...
were decided by the operator based on the angio-
gram findings after NTG administration.

2.3. Study end points
The end points were the changes in lesion
length, reference vessel diameter, minimal lumen
diameter, and diameter stenosis after intracor-
ony NTG injection using two-dimensional quan-
titative coronary analysis (QCA). Coronary
angiographies were analyzed using the Cardio-
vascular Angiography Analysis System (CAAS
5.10, Pie Medical Imaging B.V., Maastricht, The
Netherlands) by an independent investigator
who was blinded to the clinical data. After achiev-
ing TIMI 3 flow in the culprit vessel with or with-
out mechanical reperfusion, lesion length,
reference vessel diameter, minimal lumen dia-
ter, and diameter stenosis at the culprit lesion
were measured. Following this, 200 μg of intra-
coronary NTG was injected into the culprit vessel
via the guiding catheter. After a time interval of at
least 1 minute, lesion length, reference vessel
diameter, minimal lumen diameter, and diameter
stenosis at the culprit lesion were measured again
in the same coronary angiographic view. An NTG
responder was defined as the lesion with a
decrease in diameter stenosis ≥4% after NTG
injection, whereas NTG nonresponder was the
lesion that did not meet this criterion.

2.4. Statistical analysis
All statistical analyses were conducted using
SPSS (version 18.0; SPSS Inc., Chicago, IL, USA).
Categorical variables were described as counts

| Table 1. Clinical, angiographic, and procedural characteristics. |
|-----------------------|------------------|------------------|---|
|                        | Responder (n = 56) | Nonresponder (n = 44) | p  |
|-----------------------|------------------|------------------|---|
| Age (y)               | 55.6 ± 11.2      | 56.9 ± 10.9      | 0.552 |
| Male, n (%)           | 48 (85.7)        | 36 (81.8)        | 0.598 |
| Risk factors, n (%)  |                  |                  |     |
| Hypertension          | 15 (26.8)        | 15 (34.1)        | 0.429 |
| Dyslipidemia          | 31 (55.4)        | 22 (50.0)        | 0.594 |
| Diabetes mellitus     | 6 (10.7)         | 11 (25.0)        | 0.059 |
| Current smoker        | 19 (33.9)        | 21 (47.7)        | 0.162 |
| Family history        | 4 (7.1)          | 7 (15.9)         | 0.206 |
| Previous MI           | 1 (1.8)          | 0 (0.0)          | <0.999 |
| Previous PCI          | 1 (1.8)          | 1 (2.3)          | <0.999 |
| Baseline lipid profile (mg/dL) |         |                  |     |
| Total cholesterol     | 210.5 ± 39.7     | 190.1 ± 41.6     | 0.014 |
| HDL cholesterol       | 39.8 ± 9.0       | 41.3 ± 11.9      | 0.472 |
| LDL cholesterol       | 128.2 ± 28.3     | 104.5 ± 37.2     | 0.001 |
| Triglyceride          | 145.1 ± 87.7     | 130.5 ± 139.1    | 0.524 |
| Creatinine            | 1.0 ± 0.2        | 1.1 ± 0.3        | 0.080 |
| Ejection fraction (%) | 54.7 ± 8.9       | 52.3 ± 9.5       | 0.194 |
| Angiogram time interval (min) | 1.4 ± 0.7 | 1.5 ± 1.0 | 0.758 |
| Location of culprit lesion, n (%) |         |                  |     |
| Left anterior descending | 26 (46.4) | 24 (54.5) | 0.717 |
| Left circumflex       | 8 (14.3)         | 5 (11.4)         |     |
| Right coronary        | 22 (39.3)        | 15 (34.1)        |     |
| No. of diseased vessels |                  |                  | 0.347 |
| 1                     | 30 (53.6)        | 23 (52.3)        |     |
| 2                     | 20 (35.7)        | 12 (27.3)        |     |
| 3                     | 6 (10.7)         | 9 (20.5)         |     |
| Treatment used        |                  |                  |     |
| Thrombus aspiration   | 40 (71.4)        | 28 (65.1)        | 0.502 |
| Drug-eluting stent    | 54 (98.2)        | 42 (97.7)        | <0.999 |
| Stent                 |                  |                  |     |
| No. of implanted stents | 1.1 ± 0.3 | 1.2 ± 0.5 | 0.192 |
| Diameter of stent (mm)| 3.3 ± 0.4        | 3.4 ± 0.4        | 0.102 |
| Total length of stent (mm) | 27.4 ± 11.6 | 33.7 ± 16.8 | 0.042 |

Values are presented as n (%), mean ± standard deviation.
HDL = high density lipoprotein; LDL = low density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.
and proportions and the comparisons were performed with the Chi-square tests or Fisher’s exact test. Continuous variables were presented as mean ± standard deviation. The differences in means of continuous measurements were examined using the independent samples’ t test and nonparametric Mann–Whitney U test for two-group comparisons. All p values were two-sided analysis with statistical significance level of 0.05.

3. Results

3.1. Patient and procedural characteristics

One hundred patients with 100 lesions were included in this study (Fig. 1). The clinical, angiographic, and procedural characteristics according to the change of diameter stenosis with intracoronary NTG injection are described in Table 1.

The mean age of patients was 56.1 ± 11.0 years and 84% were men. There was no significant difference in clinical characteristics between NTG responder and nonresponder groups. Culprit lesions were mainly located at the left anterior descending artery (50%), followed by the right coronary artery (37%), and left circumflex artery (13%). Thrombus aspiration was required to achieve TIMI 3 flow in 68 patients. After thrombus aspiration, there were no strokes or any complications. Four lesions had insignificant stenosis after thrombus aspiration and did not have stents implanted, two in NTG responder group and two in the nonresponder group. Only drug-eluting stents (Xience (Abbott Vascular, Santa Clara, California, USA) and Endeavor stents (Medtronic Vascular, Santa Rosa, California, USA)) were used. There was no difference in the baseline lesion lengths before NTG administration in the NTG responder and nonresponder groups respectively (23.2 ± 6.1 mm vs. 25.2 ± 8.7 mm, p = 0.193). The lesion length was significantly decreased after NTG injection in the responder group, and the reference vessel diameter and minimal lumen diameter were improved after NTG injection in both groups. The diameter of stenosis was improved after NTG injection in the responder group. The number of stents and the mean diameter of stent used were not different but the total stent length was significantly shorter in the responder group compared with the nonresponder group (27.4 ± 11.6 mm vs. 33.7 ± 11.6 mm, p = 0.042).

3.2. End points

The mean time interval between baseline and repeat QCA findings following intracoronary NTG injection was 1.45 ± 0.87 minutes (median 1.0 minutes; Interquartile range: 1.0–2.0). Table 2 shows the change in the lesion length, reference vessel diameter, minimal lumen diameter, and diameter stenosis before and after NTG injection. The lesion length significantly decreased after NTG injection (24.1 ± 7.4 mm vs. 23.4 ± 7.6 mm, p = 0.001), and the reference vessel diameter and minimal lumen diameter increased significantly after NTG administration (2.7 ± 0.5 mm vs. 2.9 ± 0.5 mm, p < 0.001 and 0.9 ± 0.4 mm vs. 1.2 ± 0.5 mm, p < 0.001, respectively). The diameter stenosis also decreased significantly (66.6 ± 14.8% vs. 58.3 ± 16.1%, p < 0.001). A representative case is described in Fig. 2.

The QCA analysis of responders and nonresponders before and after NTG injection is shown in Table 3.

4. Discussion

The main findings from this study are: (1) the lesion length and the diameter stenosis signifi-

Figure 2. A representative case of ST-elevation myocardial infarction. A 57-year-old current male smoker was referred to our institution for chest pain at rest. Electrocardiogram showed ST-segment elevation in lead II, III, and aVF. (A) Coronary angiography showed total occlusion with thrombus in the middle segment of the right coronary artery (mRCA); (B) after thrombus aspiration, antegrade flow was normalized and the culprit lesion was seen with a diffuse long lesion; (C) however, intracoronary injection of 200 µg nitroglycerin resulted in the reduction of lesion length of the culprit lesion; (D) finally, a short single stent was implanted for the culprit lesion.
cantly decreased following intracoronary NTG injection; (2) the reference vessel diameter and the minimal lumen diameter increased after NTG injection; and (3) the total stent length was significantly shorter in the NTG responder group compared with the nonresponder group even though the baseline lesion lengths before NTG administration were similar.

The findings indicate that the angiographic assessment of stenosis severity of atherothrombotic culprit lesions in STEMI patients may be overestimated due to the presence of the vasoconstrictor component even after the restored antegrade blood flow. A routine pretreatment with intracoronary NTG injection is recommended to unmask vasoconstriction, to assess the true vessel size and to reduce the risk of vasoconstrictor reactions during the procedure [1]. Most patients with STEMI have some degree of coronary vasoconstriction and therefore intracoronary administration of NTG is recommended before starting the coronary angiographic sequence used for stent size selection [2]. The presence of thrombus can also lead to stent undersizing (or otherwise suboptimal deployment), which is a frequent cause of restenosis or stent thrombosis in real-life practice. Although the disruption of coronary atherosclerotic plaque complicated by thrombosis is the most common pathophysiological mechanism of acute coronary syndrome (ACS), coronary artery vasoconstriction is also considered an important causative factor in the pathogenesis of ACS [3]. At present however, there is little information on the prevalence and clinical features of coronary vasoconstriction in patients with ACS [4], especially in STEMI patients [5]. A recent study reported that 20% of patients presenting with ACS without obstructive coronary artery disease had coronary vasoconstriction in response to intracoronary administration of acetylcholine [6], suggesting that coronary vasoconstriction is an important factor in ACS.

There is uncertainty regarding the cause–effect relationship between the occurrence of coronary vasoconstriction and thrombus formation [7]. However, what is known is that coronary vasoconstriction can cause coronary plaque progression and rupture of vulnerable plaques [8,9], even in nonculprit vessels during PCI in STEMI patients [10]. Furthermore, prolonged coronary vasoconstriction can induce a limitation to coronary flow, which can trigger acute thrombus formation through the activation of platelets and various adhesion molecules as well as fibrin formation [9]. In a previous study, which enrolled 240 ACS patients and examined 701 coronary arteries, atherothrombotic occlusive lesions were observed significantly more in spasm-positive compared with spasm-negative coronary arteries [11]. Although the cause–effect relationship between vasoconstriction and atherothrombotic lesions in ACS remains uncertain, a vasoconstrictor component may contribute to an overestimation in the severity of the coronary occlusion and thus pose
management challenges. For multivessel disease during primary PCI for STEMI, current guidelines state that PCI during the acute event should be limited to the infarct-related artery (culprit vessel), with the exception of those patients with cardiogenic shock and critical stenosis or highly unstable lesions at nonculprit vessels [12]. Complete revascularization at the index procedure could expose the patient to additional and unnecessary risks including a longer procedure and increased contrast doses because of an overestimation of stenosis severity caused by vasoconstriction, which can occur in the acute STEMI setting [12].

NTG is a vasodilator that acts independently to the vascular endothelium by the intracellular production of nitric acid, resulting in relaxation of smooth muscle cells [13–15]. The resolution of vasoconstriction and the large thrombus burden associated with ACS in the first few hours to days after PCI may lead to stent undersizing and malapposition, which subsequently can lead to stent thrombosis or restenosis [16]. Studies have therefore emphasized the importance of correct sizing of stents, especially in those with a substantial thrombus burden and vasoconstriction [16–18]. The ability to optimize stent deployment not only improves clinical outcomes but can also be cost saving [19]. A previous study found the presence of vasoconstriction in nearly a third of culprit lesions in ACS patients treated with PCI. However, the vasoconstrictor component was assessed days after PCI was performed [11]. In the present study, we assessed the vasoconstrictor component in culprit lesions with normal antegrade blood flow prior to PCI. The significant decrease in lesion length and increases in reference vessel diameter and minimal lumen diameter after NTG injection support the presence of a vasoconstrictor component in patients with STEMI. Moreover, there was also a decrease of the total stent length and a trend towards implanting fewer stents in culprit lesions of responders compared with nonresponders. This implies that the application of intracoronary NTG prior to deciding stent size may assist in the selection of the most appropriate stent length and size, and thus may avoid additional stenting and stent malapposition.

The mean time interval between baseline and repeat QCA findings was 1.45 ± 0.87 minutes. It is essential that operators performing primary PCI in STEMI patients act rapidly to restore coronary blood flow in the occluded artery to stop evolving ischemia. However, once TIMI 3 flow has been restored, time can be taken to ensure an appropriate stent is selected. In an intravascular ultrasound (IVUS) study, there appeared to be a higher incidence of stent malapposition in STEMI compared with stable angina [20]. In stable patients, the incidence of stent malapposition was 4–22% [21], whereas further IVUS study of STEMI patients reported stent malapposition at 33–39% [22]. An independent predictor of acute stent malapposition is stent underexpansion caused by inappropriate sizing, which has been associated with stent thrombosis and restenosis [17,19]. Although thrombus resolution, plaque regression, and positive remodeling are the main causes of late stent malapposition, vasoconstrictor component at the index event may be a possible cause of late stent malapposition.

In the present study, although we included patients with TIMI 3 antegrade flow after balloon angioplasty and thrombus aspiration, these patients showed a larger vessel size after NTG injection. Therefore, the use of NTG prior to stenting in STEMI culprit lesions can help overcome coronary vasoconstriction and thereby enable a better assessment of the vessel size for final stent sizing by the operator.

4.1. Study limitations

This study has some limitations. Firstly, selection bias may have occurred in individual cases. Only patients achieving at least TIMI 3 following balloon angioplasty and thrombus aspiration were included in the study. This was a requirement as the lumen size is dependent on coronary flow velocity [23], and our intention was to assess the vasoconstrictor component in the STEMI culprit lesions by angiography. In other words, we first tried to normalize the antegrade flow, minimize the effect of flow dependent vessel size change, and then identify the vasoconstrictor component using NTG injection. Secondly, the nature of this registry does not allow for comparison with a reference technique. Thus, it is essential to perform a prospective randomized trial to compare the acute and late stent malapposition rates using intravascular imaging modalities such as IVUS or optical coherence tomography and the clinical outcomes of angiographic assessment with or without vasodilator use prior to PCI.

5. Conclusion

This study showed the presence of a vasoconstrictor component of atherothrombotic culprit lesions in STEMI patients receiving primary PCI.
This vasoconstrictor component should be given consideration even in emergent STEMI patients. The administration of intracoronary vasodilator such as NTG prior to stent implantation will enable appropriate and adequate stent sizing.

References

[1] Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, et al.. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2005;26:804–47.

[2] Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al.. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.

[3] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 1992;326:242–50.

[4] Maseri A, L’Abbate A, Baroldi G, Chierchia S, Marzilli M, Ballestra AM, et al.. Coronary vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study of “preinfarction” angina. N Engl J Med 1978;299:1271–7.

[5] DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, et al.. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897–902.

[6] Kaikita K, Ogawa H, Yasue H, Sakamoto T, Suefui H, Sumida H, et al.. Soluble P-selectin is released into the coronary circulation after coronary spasm. Circulation 1995;92:1726–30.

[7] Oshima S, Yasue H, Ogawa H, Okumura K, Matsuyama K. Fibrinopeptide A is released into the coronary circulation after coronary spasm. Circulation 1990;82:2222–5.

[8] Morimoto S, Shiga Y, Hiramitsu S, Yamada K, Nomura S, Miyagi Y, et al.. Plaque rupture possibly induced by coronary spasm-an autopsy case of acute myocardial infarction. Circ J 1988;52:1286–92.

[9] Nakayama N, Kaikita K, Fukunaga T, Matsuzawa Y, Sato K, Horio E, et al.. Clinical features and prognosis of patients with coronary spasm-induced non-ST-segment elevation acute coronary syndrome. J Am Heart Assoc 2014;3:e000795.

[10] Buccheri D, Carità P, Carella M, Piraino D, Chirco PR, Andolina G. Acute and spontaneous coronary thrombosis in nonculprit artery during percutaneous coronary intervention in myocardial infarction with ST-segment elevation: a “shocking” case. Int J Cardiol Heart Vasc 2015;9:52–4.

[11] Wakabayashi K, Suzuki H, Honda Y, Wakatsuki D, Kawachi K, Ota K, et al.. Provoked coronary spasm predicts adverse outcome in patients with acute myocardial infarction: a novel predictor of prognosis after acute myocardial infarction. J Am Coll Cardiol 2008;52:18–22.

[12] Ruqqieri A, Piraino D, Dendrakis G, Cortese B, Carella M, Buccheri D, et al.. STEMI patients and nonculprit lesions: to treat or not to treat? and when? A review of most recent literature. Catheter Cardiovasc Interv 2016;87:1258–68.

[13] Caramori PR, Zago AJ. Endothelial dysfunction and coronary artery disease. Arq Bras Cardiol 2000;75:163–82.

[14] Drexler H, Zeiher AM, Wollschlager H, Meinertz T, Just H, Bonzel T. Flow-dependent coronary artery dilatation in humans. Circulation 1989;80:466–74.

[15] Sinoway LI, Hendrickson C, Davidson Jr WR, Prophet S, Zelis R. Characteristics of flow-mediated brachial artery vasodilation in human subjects. Circ Res 1989;64:32–42.

[16] van Geuns RJ, Tamburino C, Fajadet J, Vrolix M, Caramori PR, Zago AJ. Endothelial dysfunction and coronary artery disease. Arq Bras Cardiol 2000;75:163–82.

[17] Maseri A, L’Abbate A, Baroldi G, Chierchia S, Marzilli M, Ballestra AM, et al.. Coronary vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study of “preinfarction” angina. N Engl J Med 1978;299:1271–7.

[18] DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, et al.. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897–902.

[19] Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, et al.. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 2007;115:2426–34.

[20] Fitzgerald PJ, Oshima A, Hayase M, Metz JA, Bailey SR, Baim DS, et al.. Final results of the Can Routine Ultrasound Stent Expansion (CRUISE) study. Circulation 2000;102:523–30.

[21] Guo N, Maehara A, Mintz GS, He Y, Xu K, Wu X, et al.. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation 2010;122:1077–84.

[22] Uren NG, Schwartzkopf SP, Metz JA, Lee DP, Honda Y, Yeung AC, et al.. Predictors and outcomes of stent thrombosis: an intravascular ultrasound registry. Eur Heart J 2002;23:124–32.

[23] Anderson HV, Stokes MJ, Leon M, Abu-Halawa SA, Stuart Y, Kirkeide RL. Coronary artery flow velocity is related to lumen area and regional left ventricular mass. Circulation 2000;102:48–54.