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Nitroglycerine-induced vasodilation in coronary and brachial arteries in patients with suspected coronary artery disease☆,☆☆

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ABSTRACT

Background: Nitroglycerine-induced vasodilation, an index of endothelium-independent vasodilation, is measured for the assessment of vascular smooth muscle cell function or alterations of vascular structure. Both coronary and brachial artery responses to nitroglycerine have been demonstrated to be independent prognostic markers of cardiovascular events. The purpose of this study was to evaluate the nitroglycerine-induced vasodilation in coronary and brachial arteries in the same patients.
Methods: We measured nitroglycerine-induced vasodilation in coronary and brachial arteries in 30 subjects with suspected coronary artery disease who underwent coronary angiography (19 men and 11 women; mean age, 69.0 ± 8.8 years; age range, 42–85 years).
Results and conclusions: The mean values of nitroglycerine-induced vasodilation in the brachial artery, left anterior descending coronary artery, and left circumflex coronary artery were 12.6 ± 5.2%, 11.6 ± 10.3%, and 11.9 ± 11.0%, respectively. Nitroglycerine-induced vasodilation in the brachial artery correlated significantly with that in the left anterior descending coronary artery ($r = 0.43$, $P = 0.02$) and that in the left circumflex coronary artery ($r = 0.49$, $P = 0.006$). There was also a significant correlation between nitroglycerine-induced vasodilation in the left anterior descending coronary artery and that in the left circumflex coronary artery ($r = 0.72$, $P < 0.001$). These findings suggest that vascular smooth muscle cell dysfunction is a systemic disorder and thus impairment of endothelium-independent vasodilation in peripheral arteries and that in coronary arteries are simultaneously present. Nitroglycerine-induced vasodilation in the brachial artery could be used as a surrogate for that in a coronary artery and as a prognostic marker for cardiovascular events.

1. Introduction

In diagnostic coronary angiography, nitroglycerine is routinely administered into a coronary artery to examine whether the cause of luminal narrowing on angiography is associated with atherosclerotic plaque or coronary artery spasm. Coronary vasoreactivity to intracoronary administration of nitroglycerine has been reported to be impaired in patients with coronary risk factors or coronary artery disease [1]. In patients with more than 50% luminal narrowing of the right coronary artery or with patients with dyslipidemia who had minimal disease of the left anterior descending coronary artery, the response of the left anterior descending coronary artery to intracoronary administration of nitroglycerine was shown to be significantly smaller than

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that in healthy subjects or patients with dyslipidemia who had a normal coronary artery on angiography [1]. More importantly, impaired coronary vasoreactivity to intracoronary administration of nitroglycerine was shown to be associated with a significantly higher incidence of cardiovascular events [2]. In addition, patients suffering from cardiovascular events had significantly blunted vasodilatory responses to intracoronary administration of nitroglycerine [2]. These findings suggest that nitroglycerine-induced vasodilation in the coronary artery can be used as not only a diagnostic tool but also a prognostic marker of atherosclerosis in patients at risk for coronary artery disease. Although intracoronary administration of nitroglycerine enables assessment of endothelium-independent vasodilation directly in the coronary artery itself, which is a clinically important vascular bed, this method is limited by its invasive nature and it is therefore difficult to repeat assessment of nitroglycerine-induced vasodilation in the coronary artery.

Measurement of nitroglycerine-induced vasodilation in the brachial artery is usually performed for the assessment of endothelium-independent vasodilation as a control test for flow-mediated vasodilation (FMD) in the brachial artery to assure that the vascular response to hyperemia is not influenced by underlying vascular smooth muscle cell dysfunction or alterations of vascular structure but truly a consequence of endothelium-dependent vasodilation [3–5]. Nitroglycerine-induced vasodilation in the brachial artery per se has been demonstrated to be impaired in patients with multiple cardiovascular risk factors or established cardiovascular disease [6–9]. In addition, we recently demonstrated that nitroglycerine-induced vasodilation in the brachial artery could be used as a prognostic marker for cardiovascular events [10]. However, there is little information on the relationship between nitroglycerine-induced vasodilation in a coronary artery and that in the brachial artery. The purpose of this study was to investigate the relationship between nitroglycerine-induced vasodilation in the coronary artery, determined by coronary vasoreactivity to intracoronary injection of nitroglycerine, and nitroglycerine-induced vasodilation in the brachial artery, assessed by sublingual administration of a nitroglycerine tablet, in the same patients with suspected coronary artery disease who underwent coronary angiography. It would be clinically useful to know how closely nitroglycerine-induced vasodilation in the brachial artery reflects coronary vasoreactivity to intracoronary administration of nitroglycerine.

2. Material and methods

2.1. Subjects

We studied 37 consecutive patients with suspected coronary artery disease who underwent coronary angiography. Patients who received nitrate treatment ($n = 2$), who had been diagnosed with vasospastic angina ($n = 2$), who had chronic total occlusion in the left anterior descending coronary or left circumflex coronary artery ($n = 2$), and who were prescribed steroid prophylaxis for allergic reaction to iodinated contrast media before coronary angiography ($n = 1$) were excluded from the study. Finally, 30 patients (19 men and 11 women; mean age, 69.0 ± 8.8 years; age range, 42–85 years) were enrolled in this study. Hypertension was defined as treatment with oral antihypertensive agents or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, in a sitting position, on at least 3 different occasions [11]. Diabetes was defined according to the American Diabetes Association recommendation [12]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [13]. Coronary artery disease included angina pectoris with a history of percutaneous coronary intervention before or during hospitalization and prior myocardial infarction. Cerebrovascular disease included ischemic stroke, hemorrhagic stroke, and transient ischemic attack. Peripheral artery disease was defined as current intermittent claudication with ankle-brachial index <0.9 or history of previous intervention, including angioplasty and bypass graft. The study protocol conformed to the ethical guideline of the 1975 Declaration of Helsinki as reflected in a priori approval by the ethical committees of our institutions. Written informed consent for participation in the study was obtained from all subjects.

2.2. Measurement of nitroglycerine-induced vasodilation in the brachial artery

We measured vascular responses to sublingually administered nitroglycerine in the brachial artery. The subjects fasted the previous night for at least 12 h. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22–25 °C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. Thirty minutes after maintaining the supine position, nitroglycerine-induced vasodilation in the brachial artery was measured. The observers were blind to the form of examination.

A high-resolution linear artery transducer was coupled to computer-assisted analysis software (UNEXEF18G, UNEX Co, Nagoya, Japan) that used an automated edge detection system for measurement of brachial artery diameter. The brachial artery was scanned longitudinally 5–10 cm above the elbow. When the clearest B-mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained, the transducer was held at the same point throughout the scan by a special probe holder (UNEX Co) to ensure consistency of the image. Depth and gain setting were set to optimize the images of the arterial lumen wall interface. When the tracking gate was placed on the intima, the artery diameter was automatically tracked, and the waveform of diameter changes over the cardiac cycle was displayed in real time using the tracking system. This allowed the ultrasound images to be optimized at the start of the scan and the transducer position to be adjusted immediately for optimal tracking performance throughout the scan. After the baseline longitudinal image of the artery was acquired for 30 s, a sublingual tablet (75 μg nitroglycerine) was given, and images of the artery were recorded continuously until the dilation reached a plateau after administration of nitroglycerine. Subjects in whom the sublingually administered nitroglycerine tablet was not dissolved during the measurement were excluded from this study. Nitroglycerine-induced vasodilation was automatically calculated as a percent change in peak vessel diameter from the baseline value. Percentage of nitroglycerine-induced vasodilation [(Peak diameter − Baseline diameter)/Baseline diameter] was used for analysis.

2.3. Measurement of nitroglycerine-induced vasodilation in the coronary artery

Diagnostic coronary angiography was performed using a standard percutaneous radial artery approach. Quantitative coronary angiographic images of left anterior descending coronary artery and left circumflex coronary artery were obtained before and after intracoronary injection of isosorbide dinitrate with particular attention to avoid overlapping of coronary segments. After control angiography, isosorbide dinitrate (1.0 mg) was injected directly into the left main coronary by the catheter. One min after the intracoronary injection of isosorbide dinitrate, an angiogram was then obtained to assess the vasodilatory capability of the coronary arteries. The proximal portion of the left anterior descending coronary artery and the left circumflex coronary artery were used for measurement of nitroglycerine-induced vasodilation in the coronary artery.

Six- to eight-millimeter segments of the proximal left anterior descending coronary artery and left circumflex coronary artery were selected for quantitative analysis [1]. The mean diameter of the each segment was measured in the end-diastolic frame using the quantitative coronary angiography (QCA) analysis software program (QCA-CMS v.6.0, Medis, Leiden, Netherlands). A series of diameter measurements

were obtained for each scanline of the arterial segment in which diameter versus segment length was plotted in graph. The mean diameter of the segment of interest was automatically measured. For each of the left anterior descending coronary artery and left circumflex coronary artery, nitroglycerine-induced vasodilation was calculated as the percentage change in the mean coronary artery diameter after intracoronary injection of isosorbide dinitrate from the baseline value. Percentage of nitroglycerine-induced vasodilation in the coronary artery [(Mean coronary artery diameter after injection of isosorbide dinitrate − Mean baseline coronary artery diameter) / Mean baseline coronary artery diameter] were used for analysis. Left anterior descending coronary artery with luminal narrowing more than 50% in the proximal segment was excluded from the analysis (n = 1). There was no patient with coronary stent implantation in the proximal segment of left anterior descending coronary artery or left circumflex coronary artery. Both vascular tests were performed within 48 h.

2.4. Statistical analysis

Results are presented as means ± SD. All reported probability values were 2-sided, and a probability value of <0.05 was considered statistically significant. Univariate linear regression analyses were performed to assess the relationships among the nitroglycerine-induced vasodilation in the brachial artery, left anterior descending coronary artery, and left circumflex coronary artery. The data were processed using JMP version 11 (SAS institute, Cary, NC).

3. Results

3.1. Baseline clinical characteristics

The baseline clinical characteristics are summarized in Table 1. Of the 30 subjects, 19 (63.3%) were men and 11 (36.7%) were women. Eight (26.7%) had previous myocardial infarction and 26 (86.7%) had significant coronary artery stenosis (>50% luminal stenosis) on angiography. As for other complications, 3 (10.0%) had cerebrovascular disease and 4 (13.3%) had peripheral artery disease. A total of 23 (76.7%) patients had established cardiovascular diseases, including coronary artery disease, cerebrovascular disease, and peripheral artery disease.

3.2. Vascular parameters

In 2 subjects, baseline vessel diameter and nitroglycerine-induced vasodilation in the left anterior descending coronary artery could not be assessed due to overlapping of coronary segments. The mean baseline diameters of the brachial artery, left anterior descending coronary artery, and left circumflex coronary artery were 4.22 ± 0.60 mm, 2.73 ± 0.48 mm, and 2.70 ± 0.54 mm, respectively. The mean values of nitroglycerine-induced vasodilation in the brachial artery, left anterior descending coronary artery, and left circumflex coronary artery were 12.6 ± 5.2%, 11.6 ± 10.3%, and 11.9 ± 11.0%, respectively.

3.3. Relationships among nitroglycerine-induced vasodilation in the brachial artery, left anterior descending coronary artery, and left circumflex coronary artery

We divided the subjects into two groups according to the division points for the lowest tertile and middle tertile of nitroglycerine-induced vasodilation in the left anterior descending coronary artery or left circumflex coronary artery. Nitroglycerine-induced vasodilation in the brachial artery was significantly smaller in the lowest tertile than in the middle and highest tertile divided on the basis of nitroglycerine-induced vasodilation in the left anterior descending coronary artery (10.1 ± 3.5% vs. 14.4 ± 5.5%, P = 0.04) or left circumflex coronary artery (8.6 ± 4.3% vs. 14.6 ± 4.5%, P = 0.002) (Fig. 1).

Table 1
Clinical characteristics of the subjects.

Variables	n = 30
Age, y	69.0 ± 8.8
Male, n (%)	19 (63.3)
Body mass index, kg/m^2	24.9 ± 3.3
Systolic blood pressure, mmHg	127.1 ± 19.0
Diastolic blood pressure, mmHg	76.9 ± 10.9
Heart rate, bpm	67.0 ± 10.3
Creatinine, μmol/L	126.1 ± 164.2
Total cholesterol, mmol/L	4.61 ± 0.93
Triglycerides, mmol/L	1.49 ± 0.85
HDL cholesterol, mmol/L	1.50 ± 0.45
LDL cholesterol, mmol/L	2.62 ± 0.97
Glucose, mmol/L	6.39 ± 2.19
HbA1c, %	5.7 ± 1.0
Current smoking, n (%)	3 (10.0)
Complications, n (%)	
Hypertension	19 (63.3)
Dyslipidemia	22 (73.3)
Diabetes mellitus	6 (20.0)
Prior myocardial infarction	8 (26.7)
Prior coronary intervention	9 (30.0)
Angiographic stenosis of >50%	26 (86.7)
Cerebrovascular disease	3 (10.0)
Peripheral artery disease	4 (13.3)
Hemodialysis	2 (6.7)
Medication use, n (%)	
Antiplatelet drug	24 (80.0)
Antihypertensive drug	16 (53.3)
Antidiabetic drug	5 (6.6)
Statin	26 (86.7)
Insulin	1 (3.3)

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

The correlations of nitroglycerine-induced vasodilation in the brachial artery with that in the left anterior descending coronary artery and that in the left circumflex coronary artery are presented in Fig. 2A and B, respectively. Univariate regression analysis revealed that nitroglycerine-induced vasodilation in the brachial artery correlated significantly with that in the left anterior descending coronary artery (r = 0.43, P = 0.02) (Fig. 2A) and that in the left circumflex coronary artery (r = 0.49, P = 0.006) (Fig. 2B). There was also a significant correlation between nitroglycerine-induced vasodilation in the left anterior descending coronary artery and that in the left circumflex coronary artery (r = 0.72, P < 0.001).

4. Discussion

We investigated the relationship between nitroglycerine-induced vasodilation in coronary and brachial arteries in patients with suspected coronary artery disease, including patients who actually had significant coronary artery stenosis on angiography. In the present study, we demonstrated that nitroglycerine-induced vasodilation in the brachial artery correlated significantly with that in the left anterior descending coronary artery and that in the left circumflex coronary artery. To our knowledge, this is the first report showing a significant correlation between nitroglycerine-induced vasodilation in coronary and brachial arteries.

Coronary epicardial and microvascular endothelial functional tests are considered as gold standard techniques for assessing endothelial function. Although these techniques enable assessment of endothelial function directly in this clinically important vascular bed, they are limited by their invasive nature and the need for special expertise and equipment, leading to difficulty in repeated measurement, especially in asymptomatic patients. An alternative endothelial functional measurement involves peripheral circulation. Measurement of FMD in the brachial artery, an index of endothelium-dependent vasodilation in a peripheral artery, has become the most widely used technique to measure endothelial function in humans as a noninvasive approach.

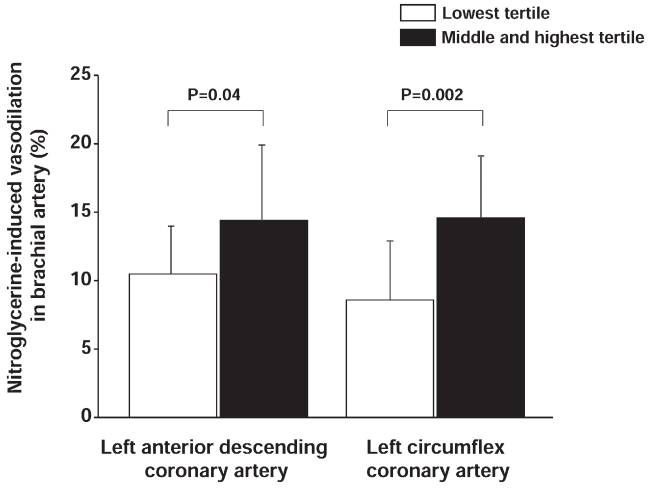

Fig. 1. Bar graph shows nitroglycerine-induced vasodilation in the brachial artery in the lowest tertile (white bar) and middle and highest tertile (black bar) divided according to the nitroglycerine-induced vasodilation in the left anterior descending coronary artery (left) and left circumflex coronary artery (right).

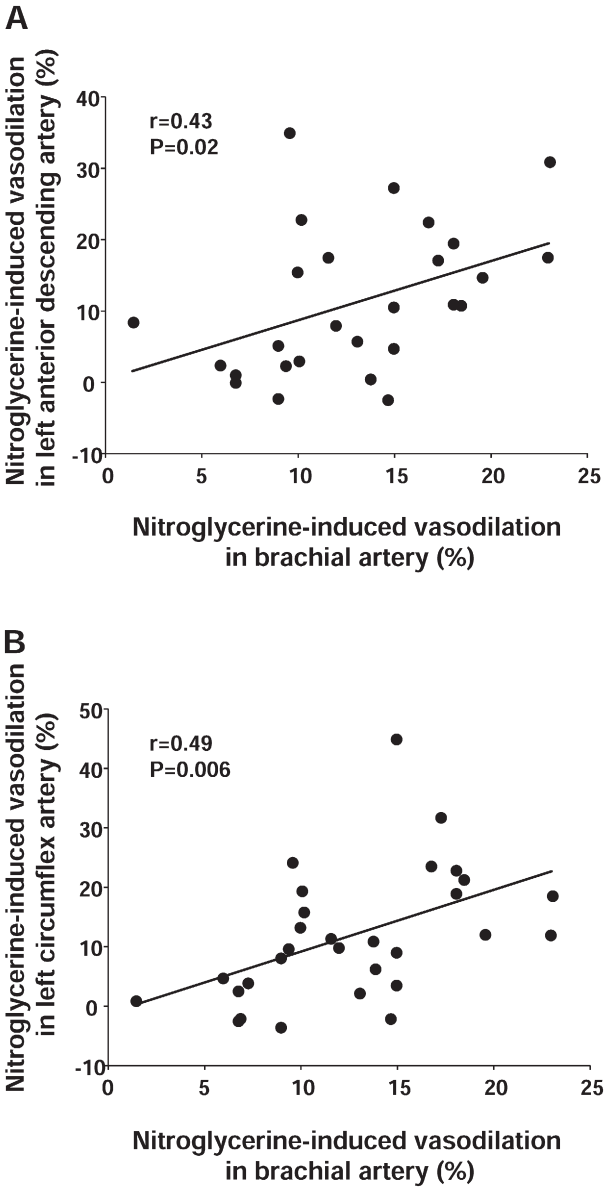

Fig. 2. Scatter plots show the relationship between nitroglycerine-induced vasodilation in the brachial artery and left anterior descending coronary artery (A) and left circumflex coronary artery (B).

Not only coronary endothelial function but also peripheral endothelial function has been shown to be independently associated with cardiovascular events with similar power to endothelial functional tests in coronary artery to predict cardiovascular events [14]. Although measurement of FMD in the brachial artery does not enable assessment of endothelial function in the coronary circulation directly, previous studies demonstrated a significant correlation between brachial and coronary endothelial function [15–17]. This association is a possible explanation for the ability of an endothelial functional test in the brachial artery to predict future cardiovascular events.

Nitroglycerine-induced vasodilation, an index of endothelium-independent vasodilation, is measured for assessment of the influence of vascular smooth muscle cell function or alterations of vascular structure on vascular response to hyperemia, as a control test for an endothelial functional test. However, nitroglycerine-induced vasodilation per se is impaired in some patients with atherosclerosis. Zeiher et al. [1] showed that the response of the left anterior descending coronary artery to intracoronary administration of nitroglycerine was significantly smaller in patients with minimal disease of the left anterior descending coronary artery than in subjects with a normal coronary artery on angiography. Moreover, Schachinger et al. [2] demonstrated that not only impaired coronary endothelial vasoreactivity but also impaired coronary vasoreactivity to intracoronary administration of nitroglycerine was independently associated with a significantly higher incidence of cardiovascular events. Recently, we reported that nitroglycerine-induced vasodilation in the brachial artery was impaired in patients with multiple cardiovascular risk factors or established cardiovascular disease [7,8] and that nitroglycerine-induced vasodilation in the brachial artery was an independent predictor of cardiovascular events [10]. These findings suggest that both coronary artery and brachial artery responses to nitroglycerine can be used as prognostic markers of cardiovascular disease. However, there is little information on the relationship between nitroglycerine-induced vasodilation in coronary and brachial arteries. In the present study, we demonstrated that there were significant correlations between nitroglycerine-induced vasodilation in coronary and brachial arteries. Teragawa et al. [17] previously reported that nitroglycerine-induced vasodilation in a coronary artery did not correlate significantly with that in the brachial artery. Although we do not know the precise reasons for the discrepancy in the results of our study and the results of that study, one possible explanation is the difference in subject selection. Only subjects with angiographically normal epicardial coronary arteries were enrolled in the previous study [17], whereas not only subjects with angiographically normal epicardial coronary arteries but also those with significant coronary artery disease were enrolled in the present study. Actually, in the present study, 86.7% of the subjects had significant stenosis in a coronary artery on angiography and 76.7% had established cardiovascular diseases. Nitroglycerine-induced vasodilation in coronary and brachial arteries has been demonstrated to be impaired only in patients at high risk for cardiovascular disease or with established cardiovascular diseases [1,6–9]. The relatively narrow range of low-risk participants in the previous study may have resulted in no significant relationship between nitroglycerine-induced vasodilation in a coronary artery and nitroglycerine-induced vasodilation in the brachial artery [17]. In contrast, a significant correlation between coronary and brachial artery responses to nitroglycerine was detectable in the present study due to the enrollment of a wide range of subjects, including patients with advanced atherosclerosis. This significant correlation between coronary and brachial artery responses to nitroglycerine may be one of the explanations for the ability of nitroglycerine-induced vasodilation in the brachial artery to predict future cardiovascular events.

5. Limitations

Our study has a number of limitations. First, the number of subjects in the present study was relatively small. However, we found that nitroglycerine-induced vasodilation in the brachial artery correlated with that in the left anterior descending coronary artery and that in the left circumflex coronary artery in the same patients with suspected coronary artery disease who underwent coronary angiography. A more specific conclusion regarding the role of nitroglycerine-induced vasodilation in the brachial artery in a surrogate for that in a coronary artery and cardiovascular events could be drawn by investigation using a larger number of subjects, including patients with various types of angina pectoris and patients with acute coronary syndrome. Although we cannot deny the possibility that some medications affect nitroglycerine-induced vasodilation in the coronary and brachial arteries, Gokce et al. [18] showed that administration of nonnitrate vasoactive drugs had no effect on nitroglycerine-induced vasodilation in the brachia artery. In addition, we excluded patients who received nitrate treatment in the present study.

6. Conclusion

There is a significant correlation between nitroglycerine-induced vasodilation in coronary and brachial arteries in patients with suspected coronary artery disease. Our findings suggest that vascular smooth muscle cell dysfunction is a systemic disorder and thus impaired endothelium-independent vasodilation in coronary arteries and that in peripheral arteries are simultaneously present. The significant correlation between coronary and brachial artery responses to nitroglycerine supports the idea that nitroglycerine-induced vasodilation in the brachial artery could be used as a surrogate for that in a coronary artery and as a prognostic marker for cardiovascular events.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References

[1] A.M. Zeiher, H. Drexler, H. Wollschlager, H. Just, Modulation of coronary vasomotor tone in humans. Progressive endothelial dysfunction with different early stages of coronary atherosclerosis, Circulation 83 (1991) 391–401.
[2] V. Schachinger, M.B. Britten, A.M. Zeiher, Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease, Circulation 101 (2000) 1899–1906.
[3] M.C. Corretti, T.J. Anderson, E.J. Benjamin, D. Celermajer, F. Charbonneau, M.A. Creager, et al., Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force, J. Am. Coll. Cardiol. 39 (2002) 257–265.
[4] T. Inoue, H. Matsuoka, Y. Higashi, S. Ueda, M. Sata, K.E. Shimada, et al., Flow-mediated vasodilation as a diagnostic modality for vascular failure, Hypertens. Res. 31 (2008) 2105–2113.
[5] A.J. Flammer, T. Anderson, D.S. Celermajer, M.A. Creager, J. Deanfield, P. Ganz, et al., The assessment of endothelial function: from research into clinical practice, Circulation 126 (2012) 753–767.
[6] M.R. Adams, J. Robinson, R. McCredie, J.P. Seale, K.E. Sorensen, J.E. Deanfield, et al., Smooth muscle dysfunction occurs independently of impaired endothelium-dependent dilation in adults at risk of atherosclerosis, J. Am. Coll. Cardiol. 32 (1998) 123–127.
[7] T. Maruhashi, J. Soga, N. Fujimura, N. Idei, S. Mikami, Y. Iwamoto, et al., Nitroglycerine-induced vasodilation for assessment of vascular function: a comparison with flow-mediated vasodilation, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 1401–1408.
[8] T. Maruhashi, A. Nakashima, T. Matsumoto, N. Oda, Y. Iwamoto, A. Iwamoto, et al., Relationship between nitroglycerine-induced vasodilation and clinical severity of peripheral artery disease, Atherosclerosis 235 (2014) 65–70.
[9] O.T. Raitakari, J.P. Seale, D.S. Celermajer, Impaired vascular responses to nitroglycerin in subjects with coronary atherosclerosis, Am. J. Cardiol. 87 (2001) 217–219 (A8).
[10] M. Kajikawa, T. Maruhashi, E. Hida, Y. Iwamoto, T. Matsumoto, A. Iwamoto, et al., Combination of flow-mediated vasodilation and nitroglycerine-induced vasodilation is more effective for prediction of cardiovascular events, Hypertension (2016).
[11] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo Jr., et al., The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report, J. Am. Med. Assoc. 289 (2003) 2560–2572.
[12] American Diabetes Association: clinical practice recommendations 1999, Diabetes Care 22 (Suppl. 1) (1999) S1–114.
[13] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III), JAMA 285 (2001) 2486–2497.
[14] A. Lerman, A.M. Zeiher, Endothelial function: cardiac events, Circulation 111 (2005) 363–368.
[15] T.J. Anderson, A. Uehata, M.D. Gerhard, I.T. Meredith, S. Knab, D. Delagrange, et al., Close relation of endothelial function in the human coronary and peripheral circulations, J. Am. Coll. Cardiol. 26 (1995) 1235–1241.
[16] B. Takase, A. Uehata, T. Akima, T. Nagai, T. Nishioka, A. Hamabe, et al., Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease, Am. J. Cardiol. 82 (1998) 1535–1539 (A7-8).
[17] H. Teragawa, K. Ueda, K. Matsuda, M. Kimura, Y. Higashi, T. Oshima, et al., Relationship between endothelial function in the coronary and brachial arteries, Clin. Cardiol. 28 (2005) 460–466.
[18] N. Gokce, M. Holbrook, L.M. Hunter, J. Palmisano, E. Vigalok, J.F. Keaney Jr., et al., Acute effects of vasoactive drug treatment on brachial artery reactivity, J. Am. Coll. Cardiol. 40 (2002) 761–765.