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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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[6] This author is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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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