Abnormal Epicardial Coronary Resistance in Patients With Diffuse Atherosclerosis but “Normal” Coronary Angiography

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Background—Coronary arteries without focal stenosis at angiography are generally considered non–flow-limiting. However, atherosclerosis is a diffuse process that often remains invisible at angiography. Accordingly, we hypothesized that in patients with coronary artery disease, nonstenotic coronary arteries induce a decrease in pressure along their length due to diffuse coronary atherosclerosis.

Methods and Results—Coronary pressure and fractional flow reserve (FFR), as indices of coronary conductance, were obtained from 37 arteries in 10 individuals without atherosclerosis (group I) and from 106 nonstenotic arteries in 62 patients with arteriographic stenoses in another coronary artery (group II). In group I, the pressure gradient between aorta and distal coronary artery was minimal at rest (1±1 mm Hg) and during maximal hyperemia (3±3 mm Hg). Corresponding values were significantly larger in group II (5±4 mm Hg and 10±8 mm Hg, respectively; both P<0.001). The FFR was near unity (0.97±0.02; range, 0.92 to 1) in group I, indicating no resistance to flow in truly normal coronary arteries, but it was significantly lower (0.89±0.08; range, 0.69 to 1) in group II, indicating a higher resistance to flow. In 57% of arteries in group II, FFR was lower than the lowest value in group I. In 8% of arteries in group II, FFR was <0.75, the threshold for inducible ischemia.

Conclusion—Diffuse coronary atherosclerosis without focal stenosis at angiography causes a graded, continuous pressure fall along arterial length. This resistance to flow contributes to myocardial ischemia and has consequences for decision-making during percutaneous coronary interventions. (Circulation. 2001;104:2401-2406.)

Key Words: blood flow ■ pressure ■ coronary disease ■ atherosclerosis ■ angina ■ ischemia

The coronary circulation is traditionally considered a 2-compartment model. The first compartment consists of epicardial vessels, which are also referred to as “conductance vessels” because they do not oppose any resistance to blood flow. The second compartment consists of arteries <400 μm, or “resistive vessels.” In this schematic representation, when no stenosis is present, myocardial flow is primarily controlled by resistive vessels.

Pathological and intravascular ultrasound studies have shown that when a stenosis is visible at arteriography, the remainder of the coronary tree is diffusely involved by atherosclerosis, although this is often not identified by coronary arteriography.2-5 In contrast, maximal myocardial flow has been shown to decrease only when a focal diameter stenosis >50% is present in the artery.6,7 Therefore, diffuse atherosclerosis without segmental stenosis is generally perceived to have no influence on myocardial blood flow.

Although diffuse atherosclerosis without segmental stenosis is also a substrate for plaque rupture and associated unstable coronary syndromes or myocardial infarctions,8-10 its hemodynamic effects on coronary artery pressure and flow have not been previously described.

Accordingly, we hypothesized a fundamentally new concept that in patients with coronary artery disease, coronary arteries without focal stenosis have a graded, continuous decrease in intracoronary pressure along their length, reflecting the hemodynamic effects of diffuse coronary atherosclerosis, that is not found in normal controls. Confirmation of this hypothesis would extend measurements of fractional flow reserve (FFR)11,12 by pressure wire for defining the hemodynamic severity of localized stenoses to assessing the hemodynamic significance of diffuse coronary atherosclerosis for diagnostic or therapeutic purposes.
Patients

Group I consisted of 10 individuals with normal coronary angiograms without signs of myocardial ischemia who underwent cardiac catheterization for atypical chest pain (n=7), atrial septal defect (n=2), or early after transplant (n=1). Exercise ECG, dobutamine stress echocardiography, and stress perfusion scintigraphy were normal in all of them. Their coronary arteries appeared perfectly smooth on arteriogram. A total of 37 arteries were investigated in group I.

Group II consisted of 62 patients with a focal arteriographic stenosis in a coronary artery other than those investigated for the present study. In group II, 17 patients were admitted for unstable angina (Braunwald classification 2b or 3b), 29 patients for stable angina, 2 patients for silent ischemia at noninvasive stress testing, and 14 patients for atypical chest pain and dubious results at noninvasive stress testing. In 43 group II patients, angioplasty of a focal stenosis in another vessel was performed. Nineteen other patients were referred for assessing the physiological severity of angiographic stenoses of “intermediate” severity, followed by angioplasty if needed. In group II, the coronary arteries investigated by pressure wire for this study did not have any significant focal stenosis by visual examination of the angiogram and were contralateral to the stenotic arteries. A total of 106 nonstenotic arteries were investigated in group II.

The study protocol was approved by the Ethics Committees of the Onze-Lieve-Vrouwe Hospital, Aalst, Belgium and the Catharina Hospital, Eindhoven, the Netherlands. All patients gave informed consent before the study.

Catheterization and Coronary Angiography

A 6F or 7.5F arterial sheath was introduced to monitor femoral pressure. Central aortic pressure was measured through the 6F or 7F guiding catheter without side holes. The sidearm of the arterial introducer and the guiding catheter were connected to fluid-filled pressure transducers zeroed at the mid-chest level. After intracoronary administration of 0.2 mg of isosorbide dinitrate, an angiogram of the vessel under study was taken in at least 2 different projections. The arterial reference diameter was determined by quantitative coronary angiography in the proximal segment (first 15 mm) of the vessel and the distal segment in which the pressure sensor (see below) was located. Two orthogonal projections were analyzed, and the results were averaged. A 0.014-inch Pressure Wire (RadiMedica Systems) was advanced to the tip of the guiding catheter to ensure that the pressure recorded through the guiding catheter and the Pressure Wire were identical at that position. The wire was then advanced into the most distal part of the vessel.

If there had been recorded under baseline conditions, coronary arteriolar vasodilatation was induced by the intravenous administration of adenosine (140 μg · kg⁻¹ · min⁻¹, n=42) or by an intracoronary bolus of adenosine (20 to 40 μg, n=30). FFR was calculated as the ratio of distal coronary pressure to aortic pressure during maximal hyperemia. In the patients in whom steady-state hyperemia was induced by intravenous adenosine, the pressure wire was slowly pulled back from the most distal to the proximal part of the artery by manual (n=24) or motorized automatic (at a speed of 1 mm/s, n=18) pullback. When the pressure sensor was pulled back in the guiding, both pressures were checked to exclude any drift of the transducers. An example of pressure recordings in a normal and in an atherosclerotic coronary artery are illustrated in Figures 1 and 2.

FFR as an Index of Epicardial Resistance

FFR is defined as the ratio of maximal hyperemic blood flow in the presence of a stenosis divided by normal hyperemic blood flow without stenosis and is calculated as the ratio of distal coronary pressure (Pd) divided by aortic pressure (Pa) at maximum hyperemia, as follows: FFR=Pd/Pa. If there is no resistance along an artery, there is no pressure decline and FFR equals unity. The larger the resistance to blood flow, the larger the decline in pressure and, thus, the smaller FFR. Therefore, FFR as the ratio of distal to proximal coronary pressures is an index of the resistance to flow along the epicardial vessel and, conversely, 1–FFR represents to what extent (expressed in percent) the segment of epicardial artery located between the 2 measurement points (Pd and Pa, respectively) contributes to the total resistance to maximal myocardial flow.

Statistical Analysis

Results are reported as mean±SD. Differences between continuous data were tested by paired and unpaired t tests, as appropriate. Linear regression analysis was used to investigate the relation between arterial dimensions and FFR. Differences between proportional (discrete or categorical) data were tested by Fisher’s exact test.

Results

Baseline characteristics and risk factors for coronary artery disease for both patients groups are shown in Table 1. Group I subjects were younger and had significantly fewer risk factors than the patients in group II. The male/female ratio was similar.

Table 2 shows arterial dimensions and pressure-derived data. The proximal diameter of normal arteries in group I was significantly larger than that of the nonstenotic atherosclerotic arteries from group II patients. There were no significant differences between the left anterior descending coronary artery (LAD), the left circumflex artery (LCx), and the right coronary artery (RCA). In group II, the distal segments of the RCA were significantly larger (3.01±0.57 mm) than the corresponding segments in the LAD (2.11±0.44 mm) and LCx (2.30±0.48 mm). However, on average, distal arterial diameters were similar in both groups. As a consequence, the tapering (ie, the decrease in diameter between the proximal and the distal segment) was smaller in group II than in group I.

The resting pressure gradient between the central aorta and the distal part of the coronary artery was significantly smaller in normal coronary arteries (median, 1 mm Hg; range, 0 to 2 mm Hg) than in atherosclerotic coronary arteries (median, 3 mm Hg; range, 0 to 18 mm Hg). This pressure difference further increased during adenosine-induced maximal hyperemia (normal arteries: median, 3 mm Hg; range, 1 to 7 mm Hg; atherosclerotic arteries: median, 8 mm Hg; range, 0 to 31 mm Hg). The FFR measured in the distal part of normal coronary arteries (median, 0.98; range, 0.92 to 1) was significantly larger than the FFR measured in atherosclerotic arteries (median, 0.90; range, 0.69 to 1). As shown in Figure 3, 57% of the FFR values obtained for nonstenotic atherosclerotic arteries in group II patients were below the lowest value observed in normal arteries, and 8% were below the ischemic threshold value of 0.75.

No artery studied by slow pullback of the pressure wire showed a sudden increase in distal coronary pressure, indicating that the pressure gradient observed in the distal part of the artery was due to a continuous loss of pressure along the arterial length rather than to a focal narrowing not detected at angiography.

There was no relation between the FFR and proximal diameter, distal diameter, or degree of tapering of the artery, as determined by angiography. There were no differences in FFR among the 3 major coronary arteries in group I (LAD,
0.97±0.03; LCx, 0.97±0.02; RCA, 0.97±0.03). In group II, the FFR in the distal nonstenotic LAD was significantly lower (0.86±0.09) than in the nonstenotic LCx (0.91±0.08). In 25 of the group II patients, both the LAD and the LCx were investigated. In these patients, a weak correlation ($r=0.46$, $P=0.025$) was observed between FFR values for these 2 arteries in the same patient.

**Discussion**

The present study demonstrates that, in patients with coronary artery stenosis in another vessel, approximately half of coronary arteries without arteriographic focal stenosis have a graded, continuous decline in coronary pressure along their length, especially during hyperemia. This decline in pressure was not observed in the normal arteries of subjects without atherosclerosis. The presence and/or severity of this coronary pressure gradient could not be predicted from the angiogram. These results are based on directly measured coronary pressure and FFR, a well-validated specific index of epicardial conductance. The present data also confirm that there is virtually no difference in pressure (ie, no loss of energy) between proximal and distal normal coronary arteries, even at maximal coronary flow. Our results confirm and establish the mechanism for the observation by Gould et al of a graded, base-to-apex myocardial perfusion gradient after dipyridamole by positron emission tomography in patients with mild atherosclerosis and without significant regional perfusion defects. The present data indicate that this base-to-apex perfusion gradient is due, at least in part, to the abnormal resistance of atherosclerotic epicardial coronary arteries without segmental stenosis. A slow pullback of the pressure sensor from the distal to the proximal part of the arteries at maximal hyperemia did not show any discrete pressure drop. Instead, a gradual increase in distal pressure was observed, suggesting that the abnormal resistance is distributed over the whole length of the vessel. These findings have several physiological and clinical implications.

**Abnormal Resistance in Atherosclerotic Coronary Arteries**

In addition to hemodynamically significant focal stenoses in the epicardial arteries, atherosclerosis can cause myocardial ischemia by several other mechanisms. First, the ability of the coronary resistive arterioles to vasodilate maximally after physiological or pharmacological stress (“microvascular disease”) may be impaired early in the atherosclerotic process or be associated with coronary risk factors before angiographically apparent disease develops. Second, a paradoxical vasoconstriction has been well documented in atherosclerotic coronary arteries during different kinds of
stress. In addition, the present data demonstrate that more than half of atherosclerotic arteries without focal stenoses have a significantly higher resistance to flow than observed in normal arteries. In 8% of atherosclerotic arteries without segmental stenosis, FFR was even lower than the 0.75 threshold value, below which reversible myocardial ischemia is usually observed by noninvasive stress testing. The decrease in pressure observed in these arteries indicates that diffusely atherosclerotic arteries can be responsible for up to one third of the total resistance to blood flow, even though no focal stenosis is visible at angiography. Because these studies were done after the intracoronary infusion of isosorbide dinitrate, the observed resistance of diffusely atherosclerotic coronary arteries without focal stenosis is most likely due to mild diffuse structural narrowing, not to vasoconstriction.

The present study, therefore, suggests that in addition to the above mechanisms for myocardial ischemia, abnormal resistance of coronary arteries due to diffuse atherosclerosis without focal stenosis may contribute to stress-induced myocardial ischemia and flow maldistribution on perfusion scintigrams, even after vasodilation of the epicardial arteries by nitrates.

The poor correlation between FFR and arterial diameters reflects the failure of standard coronary arteriography to account for the hemodynamic effects of diffuse disease.

Although the coronary angiogram has been used as the standard for comparison with other technologies for detecting reversible myocardial ischemia, the presence of abnormal resistance to flow of atherosclerotic coronary arteries without focal stenosis on angiograms may explain some clinically typical angina pectoris or some “false-positive” results of noninvasive stress testing in the absence of angiographic focal stenosis. However, these directly measured coronary pressures are consistent with complete fluid dynamic analysis of the entire coronary arteriographic tree for diffuse disease.

Several studies have emphasized a progressive decrease in coronary flow reserve in normal individuals especially after the age of 65. This phenomenon has been ascribed to increased resting perfusion and, hence, a lower flow reserve or to progressive impairment of the resistive vessel function. The present data alternatively suggest that abnormal epicardial coronary arterial resistance due to clinically silent, mild, diffuse coronary atherosclerosis may also contribute to the progressive decline in maximal myocardial perfusion observed with age.

Implications for Coronary Stenting

As demonstrated by intravascular ultrasound, the presence of a focal stenosis at angiography is almost invariably associated with diffuse atherosclerosis of coronary vasculature. After
successful stenting of a focal stenosis, a residual hyperemic gradient may remain with an abnormal FFR if pressure is measured in the distal part of the artery. FFR measured after stenting with the pressure sensor in this distal location indicates the effects on maximal flow of the stented segment and of the remaining part of the artery. Therefore, to evaluate whether the stent has fully re-established the conductance of a previously stenotic segment, FFR should be calculated from the ratio of the pressure just distal to just proximal to the stented segment during a pullback maneuver under conditions of maximal hyperemia. This pullback pressure recording along the length of the artery indicates the conductance of the entire epicardial artery, as affected by diffuse disease (including the stented segment) and of the stenotic segment in units of mm Hg per mm of arterial length. In contrast, the pressure gradient between the 2 edges of the stent indicates the status of the stented segment alone.

**Limitations**

Intravascular ultrasound was not performed to confirm the presence of diffuse disease in arteries without focal stenosis at angiography. However, several other studies have demonstrated that the presence of a focal stenosis is almost invariably associated with atherosclerosis in the remainder of the coronary tree. In the present study, the pressure measurement during slow pullback of the sensor uniformly demonstrated a progressive decline in pressure rather than localized pressure gradients due to undetected focal stenoses. Taken together, these findings suggest that diffuse atherosclerosis is the underlying mechanism of the abnormal resistance observed along the epicardial arteries.

Resistive vessel dysfunction (which is probably present in most patients with atherosclerosis) might affect the extent to which microvascular resistance will decrease during the infusion of adenosine and, therefore, affect distal coronary pressure. Nevertheless, adenosine at the dosages used in the present study have been shown to induce maximal achievable flow in a given patient, with a given level of resistive vessel dysfunction. Therefore, distal coronary pressure [or better, \(1 - (P_d / P_a)\)] represents the extent to which the epicardial artery contributes to total resistance to (hyperemic) flow. In addition, in the hypothetical absence of microvascular dysfunction, hyperemic flow would be larger and, thus, distal coronary pressure would be lower, which would further amplify the contribution of the epicardial segments to total coronary resistance.

Electronic drift of both the fluid-filled pressure transducer (guiding) and of the distal pressure sensor (Pressure Wire)
could account for some of the pressure gradients observed. However, the strict equality of the phasic and mean pressure tracings recorded by both transducers was carefully checked before and after each measurement in each vessel.

Summary

The present study reports a new fundamental observation, namely that early stage coronary atherosclerosis is often associated with abnormal resistance of the epicardial coronary arteries before a segmental stenosis is apparent at angiography. In addition to the resistance caused by focal stenosis or by arteriolar vasomotor dysfunction, diffusely atherosclerotic epicardial coronary arteries without segmental stenosis often cause a continuous pressure decline along their length, reduce coronary flow reserve, contribute to myocardial ischemia and abnormal perfusion during exercise or pharmacological vasodilatation, and are identifiable by intracoronary pressure measurements.

References

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Circulation. 2001;104:2401-2406
doi: 10.1161/hc4501.099316
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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