# Pulse Transmission Coefficient: A Novel Nonhyperemic Parameter for Assessing the Physiological Significance of Coronary Artery Stenoses

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**OBJECTIVES** We sought to test the hypothesis that the pulse transmission coefficient (PTC) can serve as a nonhyperemic physiologic marker for the severity of coronary artery stenosis in humans.

**BACKGROUND** Coronary lesions may impair the transmission of pressure waves across a stenosis, potentially acting as a low-pass filter. The PTC is a novel nonhyperemic parameter that calculates the transmission of high-frequency components of the pressure signal through a stenosis. Thus, it may reflect the severity of the coronary artery stenosis. This study was designed to examine the correlation between PTC and fractional flow reserve (FFR) in patients with coronary artery disease.

**METHODS** Pressure signals were obtained by pressure guidewire in 56 lesions (49 patients) in the nonhyperemic state and were analyzed with a new algorithm that identifies the high-frequency components in the pressure signal. The PTC was calculated as the ratio between the distal and proximal high-frequency components of the pressure waveform across the lesion. The FFR measurements were assessed with intracoronary adenosine.

**RESULTS** There was a significant correlation between PTC and FFR ($r = 0.81$, $p < 0.001$). By using a receiver operating characteristic analysis, we identified a PTC $< 0.60$ (sensitivity 100%, specificity 98%) to be the optimal cutoff value for predicting an FFR $< 0.75$.

**CONCLUSIONS** Pulse transmission coefficient is a novel nonhyperemic parameter for the physiologic assessment of coronary artery stenoses. It correlates significantly with FFR and may predict an FFR $< 0.75$ with high accuracy. Pulse transmission coefficient may be useful as an adjunct measurement to FFR, especially in patients with microcirculatory disease and impaired maximal hyperemia. (J Am Coll Cardiol 2002;39:1012–9) © 2002 by the American College of Cardiology Foundation

Coronary angiography is currently the gold standard for assessing coronary artery disease (CAD). In many patients with CAD clinical decision-making requires an evaluation of the functional severity of the coronary lesion (1–3). The recent introduction of pressure sensor-tipped guidewires has enabled physiologic assessment of lesion severity during coronary catheterization by calculation of myocardial fractional flow reserve (FFR), which correlates with the degree of myocardial ischemia and coronary events (4–9). Thus, an intracoronary physiologic approach complements the anatomic assessment of the lesion, obtained by coronary angiography and, therefore, facilitates decision-making regarding the need for intervention.

Spectral analysis of the arterial pressure waveform has identified the dicrotic notch as a marker for high-frequency content of the pressure signal (10). Previous studies demonstrated that analysis of the pressure waveform may be associated with the degree of atherosclerotic vascular disease (11,12). More recent studies have demonstrated that aortic stenosis reduces pulse transmission, as reflected in abnormalities of carotid pulse waveform (13,14). These studies suggest that the attenuation of the high-frequency components of the pulse waveform may indicate the existence of significant flow obstruction across the lesion site. Therefore, we have assessed a novel parameter, the pulse transmission coefficient (PTC), which calculates the transmission of high-frequency components of the intracoronary pressure signal through a stenosis in the nonhyperemic state.

This current study was designed to test the hypothesis that PTC can serve as a nonhyperemic physiologic marker for the severity of coronary artery stenosis in humans, in vivo.

## METHODS

**Patient population.** The study population consisted of 49 consecutive patients (56 lesions) who were referred for coronary angiography and were found to have intermediate coronary lesions defined as 40% to 70% diameter stenosis by angiographic assessment. Exclusion criteria included: unstable angina, heart failure (ejection fraction <40%), significant left main disease (left main stenosis >50% or ostial left main disease >30%), multiple lesions in the same vessel,

> **Abbreviations and Acronyms**
> CAD = coronary artery disease
> FFR = fractional flow reserve
> PTC = pulse transmission coefficient
> QCA = quantitative coronary angiography
> ROC = receiver operating characteristic

recent myocardial infarction ($<5$ days) and significant valvular disease. The study protocol was approved by the Institutional Review Board, and a consent form was obtained from all patients.

**Study protocol.** Diagnostic coronary angiography was performed using 6F to 7F coronary catheters with the standard femoral approach after routine procedures. To avoid spasm and to achieve maximal epicardial vasodilation, sublingual (0.4 mg) or intracoronary nitroglycerin (0.1 mg to 0.3 mg) was routinely administered before initial and final angiograms and before advancement of the pressure wire across the lesion. During the procedure, heart rate was monitored and aortic pressure was recorded by the guiding catheter. Off-line quantitative coronary angiography (QCA) analysis was performed at the Mayo Clinic Core Laboratory by an investigator blinded to the results of the physiologic assessment using an automated contour detection algorithm (QCA-CMS version 5.0 MEDIS, Leiden, the Netherlands).

**Pressure measurement and calculation of FFR.** After the diagnostic coronary angiogram, the diagnostic coronary catheters were replaced by guiding catheters that were advanced through the femoral sheath to engage into the ostium of the coronary artery. Intracoronary pressure was measured with a high-fidelity pressure guidewire (0.014 in., PressureWire, Radi Medical, Uppsala, Sweden or WaveWire, EndoSonics, Rancho Cordova, California) that was first set at zero and calibrated outside the body. Aortic pressure was measured with the tip of the guiding catheter, which transmits the pressure wave to a fluid-filled pressure monitoring system. After advancing the pressure sensor (3 cm proximal to the guidewire tip) to the guiding catheter tip, the pressure signal acquired by the guidewire was compared with the fluid-filled aortic pressure and adjusted if necessary. Both the pressure wire signal and the fluid-filled aortic pressure were simultaneously fed into the SmartFlow (Florence Medical Ltd., Kfar Saba, Israel) console for the calculation of the FFR and further signal processing. The wire was initially advanced across the lesion, and the pressure-sensor was located immediately proximal to the lesion. Baseline pressures were recorded proximal to the lesion. Next, the wire was further advanced placing the pressure sensor distal to the lesion. Distal pressure was acquired both at baseline and during maximal hyperemia induced with incremental dosages of intracoronary adenosine (starting with 18 $\mu$g for the right and 24 $\mu$g for the left coronary artery). To avoid a damped aortic pressure tracing due to a catheter filled with contrast or blood, all fluid-filled pressure measurements were recorded after a saline flush of the catheters. The FFR

value was obtained in the usual fashion by calculating the ratio of the mean distal pressure to the mean proximal pressure during maximal hyperemia.

**Pressure signal processing and calculation of PTC.** The resting, or nonhyperemic, high-fidelity pressure signals obtained by the pressure guidewire were analyzed by a new algorithm (Florence Medical Ltd.) that identifies the high-frequency component in the pressure waveform. The PTC value was calculated online by the SmartFlow device algorithm as the ratio between the distal and proximal high-frequency components of the pressure signal in the nonhyperemic state (Appendix and Fig. 1). It has been previously demonstrated that FFR is less subjective to hemodynamic changes (15). Nevertheless, to avoid the possible effect of pressure dumping on the accuracy of PTC and FFR calculations, due to pre-administration of nitroglycerin, pressure recording was performed when a pressure restoration was obtained. The PTC value for each lesion was calculated as the mean of 10 consecutive pressure waveforms. Because the high-frequency components at the dicrotic notch segment, from which the PTC is derived, are at a much higher range than the respiratory or the heart rate frequencies ($>6$ Hz vs. 0.2 to 0.4 Hz or $<1$ Hz, respectively), the PTC value is not affected by either respiratory or heart rate changes.

**Statistical analysis.** All numerical data are presented as mean $\pm$SD. For the physiologic lesion analysis, the minimum obtained FFR value (maximum hyperemia) and its corresponding PTC were used. Simple linear regression analysis was used to calculate Pearson's correlation coefficients between FFR and PTC indexes of lesion severity, with their level of significance. The best fitted cutoff PTC value for predicting FFR $<0.75$ was determined by a receiver operating characteristic (ROC) curve analysis. The chi-square test for association was used to calculate the association between noninvasive functional test results and both FFR and PTC categorized values. A value of p $< 0.05$ was considered statistically significant.

## RESULTS

The study patients (n = 49) were mostly men (74%), with a mean age of 62 years (range: 43 to 83 years). The demographic and clinical characteristics of the patients are outlined in Table 1. The assessed lesions in this present study were divided into two subgroups by the PTC cutoff point of 0.6. In the subgroup with PTC $<0.6$, there were 15 patients with 16 lesions, whereas, in the subgroup with PTC $\geq0.6$, there were 34 patients with 40 lesions. There were no significant differences in age (66 vs. 60 years, respectively, p = NS) or male gender (60% vs. 79% respectively, p = NS) between the two subgroups. The distribution of risk factors as well as the clinical presentation in the two subgroups was not significantly different. The angiographic data, the results of the QCA analysis and the results of the invasive physiologic assessment of lesion
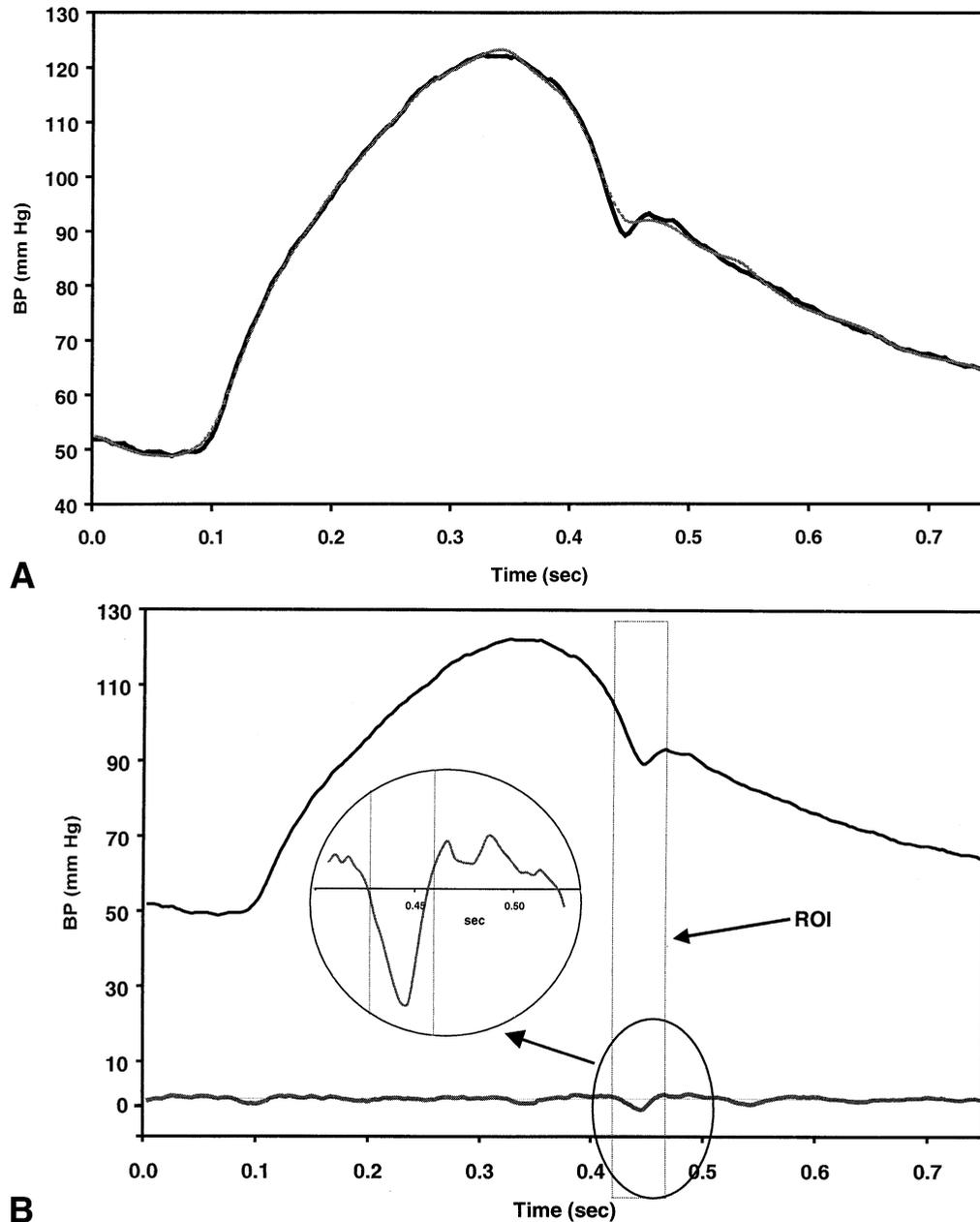
**Figure 1.** Representative plots for the measured pressure signal and the filtered signal are depicted by **solid** and **dotted lines**, respectively. The difference between the two signals is more prominent at the dicrotic notch segment **(A)**. The region of interest (ROI) **(dotted rectangle)** for the calculation of pulse transmission coefficient is defined where the change in pressure signal, which is the difference between the measured and the filtered signal (depicted at bottom), is maximum **(B)**. BP = blood pressure.

severity are outlined in Table 2. The affected vessel was the left anterior descending coronary artery in 28 (50%) lesions, the left circumflex coronary artery in 9 (16%) lesions, the right coronary artery in 16 (29%) lesions and vein graft in 3 (5%) lesions. Thirty-one (63%) patients had single-vessel disease, 12 (25%) had two-vessel disease and 6 (12%) had three-vessel disease. Overall, the mean FFR value of the assessed lesions was $0.80 \pm 0.14$, whereas the mean PTC value was $0.71 \pm 0.39$ (Table 2). Using an ROC curve analysis, in the overall cohort of 56 lesions, we identified a PTC value $<0.60$ (sensitivity 100%, specificity 98%) to be the best cutoff value for predicting an FFR value $<0.75$,

with a positive predictive power of 94% and negative predictive power of 100%. By regression analysis of the overall cohort of 56 lesions, there was a strong significant correlation between PTC and FFR ($r = 0.81$, $p < 0.001$, Fig. 2). The same results were obtained for the whole cohort of 118 observations. Moreover, all 16 lesions with PTC $<0.60$ had FFR $<0.75$, and 39 of 40 lesions with PTC $\geq0.60$ had FFR $\geq0.75$. Hyperemic frequency analysis of the pressure waveforms and the calculation of PTC did not affect the results. Precatheterization noninvasive functional tests had been performed in only 21 (43%) patients. The functional testing was positive in 19 patients and negative or

**Table 1.** Demographic and Clinical Characteristics of the Patient Population

| Variables | Study Group | | |
|---|---|---|---|
| | Total (49 pts, 56 lesions) | PTC ≥ 0.60 (34 pts, 40 lesions) | PTC < 0.60 (15 pts, 16 lesions) |
| Mean age (yrs) | 62 ± 12 | 60 ± 12 | 66 ± 12 |
| Male gender (%) | 36 (73%) | 27 (79%) | 9 (60%) |
| Risk factors for IHD (no. of patients) | | | |
| Hypertension (%) | 29 (59%) | 29 (56%) | 10 (67%) |
| Diabetes mellitus (%) | 12 (24%) | 8 (24%) | 4 (27%) |
| Hyperlipidemia (%) | 27 (55%) | 18 (53%) | 9 (60%) |
| Smoker (%) | 21 (43%) | 15 (44%) | 6 (40%) |
| Previous MI (%) | 9 (18%) | 7 (21%) | 2 (13%) |
| Previous CABG (%) | 7 (14%) | 5 (15%) | 2 (13%) |
| Family history (%) | 10 (20%) | 8 (24%) | 2 (13%) |
| Clinical presentation (no. of patients) | | | |
| Angina CCS class I (%) | 10 (20%) | 5 (15%) | 5 (33%) |
| Angina CCS class II–III (%) | 39 (80%) | 29 (85%) | 10 (67%) |

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; IHD = ischemic heart disease; MI = myocardial infarction; PTC = pulse transmission coefficient.

inconclusive in two patients. Within this subgroup, mean FFR was 0.76 ± 0.14 while mean PTC was 0.66 ± 0.41, and there was a strong significant correlation between PTC and FFR (r = 0.78, p < 0.001). However, there was no correlation between either FFR or PTC values, categorized at cutoff values of 0.75 and 0.60, respectively, and the functional test results (p = 0.29; p = 0.24 by chi-square test for association, respectively). Figure 3 shows representative coronary angiograms, coronary pressure tracings used to calculate FFR and pressure waveforms proximal and distal to the lesion used to calculate PTC, for a typical angiographically intermediate lesion.

## DISCUSSION

The present study demonstrates that the nonhyperemic frequency analysis of the intracoronary pressure waveforms may serve as a parameter for the assessment of the physiologic significance of CAD in humans. Moreover, our results

show that there is a significant correlation between PTC and FFR and that a categorized cutoff PTC value of 0.60 is an accurate index for predicting a categorized cutoff FFR value of significant stenosis.

Thus, our results suggest that PTC can serve as a nonhyperemic adjunct physiologic index for the functional assessment of intermediate lesions during coronary catheterization.

**Pressure waveform and vascular obstructive disease.** Early observations had suggested that pressure waveform analysis might be applied to evaluate the severity of atherosclerotic vascular disease. Using a classification according to the appearance of the dicrotic notch in the peripheral pressure waveform, it was demonstrated that abnormal pressure waveform with the absence of discrete dicrotic notch is associated with significant atherosclerotic vascular disease (11,12). More recently, it was shown that abnormalities in the carotid pulse waveform with alteration or

**Table 2.** Angiographic and Physiologic Characteristics of the Assessed Lesions

| Variables | Study Group | | |
|---|---|---|---|
| | Total (49 pts, 56 lesions) | PTC ≥ 0.60 (34 pts, 40 lesions) | PTC < 0.60 (15 pts, 16 lesions) |
| Affected vessel (no. of lesions) | | | |
| LAD (%) | 28 (50%) | 19 (47%) | 9 (56%) |
| LCX (%) | 9 (16%) | 6 (15%) | 3 (19%) |
| RCA (%) | 16 (29%) | 13 (33%) | 3 (19%) |
| Vein graft (%) | 3 (5%) | 2 (5%) | 1 (6%) |
| Quantitative angiography analysis | | | |
| Reference diameter (mm) | 3.14 ± 0.74 | 3.06 ± 0.72 | 3.35 ± 0.79 |
| Minimal luminal diameter (mm) | 1.43 ± 0.43 | 1.54 ± 0.46 | 1.18 ± 0.22 |
| Lesion length (mm) | 11.9 ± 7.44 | 11.02 ± 7.39 | 14.09 ± 7.34 |
| Percent diameter stenosis (%) | 53 ± 14 | 49 ± 13 | 63 ± 13 |
| Percent area stenosis (%) | 76 ± 15 | 72 ± 14 | 85 ± 11 |
| Physiologic parameters | | | |
| Mean FFR | 0.80 ± 0.14 | 0.87 ± 0.06 | 0.63 ± 0.13 |
| Mean PTC | 0.71 ± 0.39 | 0.94 ± 0.08 | 0.13 ± 0.19 |

FFR = fractional flow reserve; LAD = left anterior descending coronary artery; LCX = left circumflex artery; PTC = pulse transmission coefficient; RCA = right coronary artery.
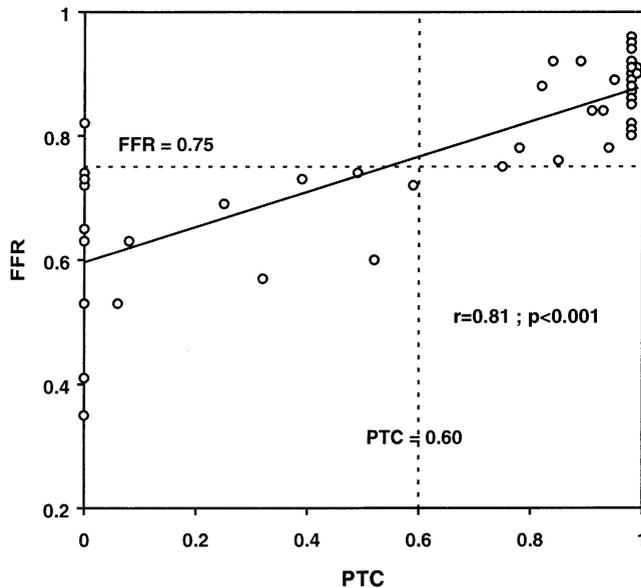
**Figure 2.** Linear correlation between pulse transmission coefficient (PTC) and fractional flow reserve (FFR). The correlation was highly significant with a high correlation coefficient. Separated by the cutoff values **(dotted lines)** of 0.75 and 0.60 for FFR and PTC, respectively, the scattered distribution of most data points is observed either in the **right upper quadrant** or in the **left lower quadrant**. This represents a good agreement between the two parameters both above and below the cutoff values.

disappearance of the dicrotic notch is highly correlated with isolated aortic stenosis (13,14). Furthermore, the absence of the dicrotic notch in the pulse pressure waveform distal to aortoiliac disease was associated with significant proximal artery stenosis, whereas its presence was found as an excellent index of normal hemodynamics (16). Based on the aforementioned observations, it seemed that spectral analysis of changes in the pressure waveform may serve as an indicator for a flow obstruction in arterial conduits.

**The high-frequency content of the pressure waveform at the dicrotic notch and PTC.** The dicrotic notch is a transient upstroke in the pressure waveform reflecting the deceleration of the arterial pressure after the closure of the aortic valve. Spectral analysis of the pressure waveform shows that the dicrotic notch segment contains numerous high-frequency components representing various reflections from the periphery (10). Therefore, the dicrotic notch segment may serve as a region of interest for the analysis of changes in the high-frequency content of pressure signal. The recent introduction of the miniature pressure wires with the acquisition of high-fidelity pressure signal across intracoronary lesions enables the application of spectral analysis of the pressure waveform with a reliable detection of the high-frequency components both proximal and distal to the lesion. Therefore, we have applied to the coronary lesion assessment a new algorithm (Florence Medical Ltd.) that can identify the high-frequency components of the pressure signal waveform at the dicrotic notch segment and calculates the PTC as the ratio between the distal and proximal
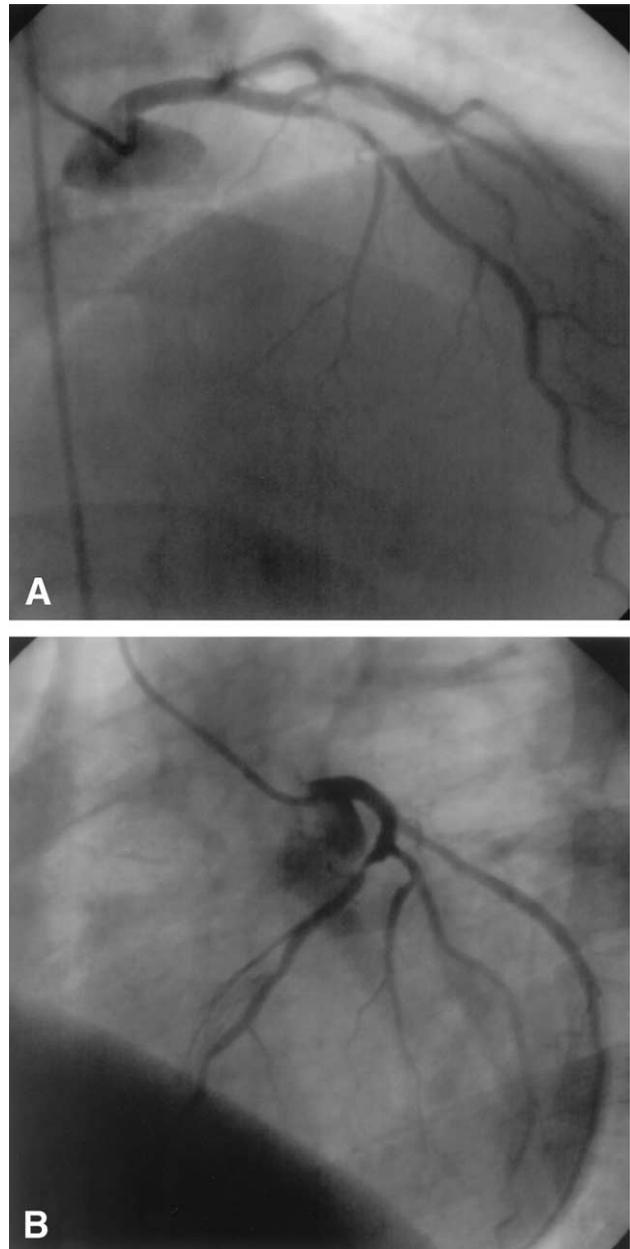


**Figure 3.** A representative coronary angiogram and simultaneous tracing of aortic and intracoronary trans-stenotic pressure signals in a 62-year-old man. The patient had angiographically intermediate stenosis (68% diameter stenosis) of the mid left anterior descending coronary artery (**A** and **B**; right anterior oblique and left anterior oblique coronary arteries projections, respectively). The pressure recordings in **C** were simultaneously obtained by the guiding catheter (fluid-filled) **(solid line)** and the pressure wire **(dotted line)**, while the sensor of the pressure wire was located both proximal and distal to the lesion. Distal pressure recording was obtained both at baseline and during adenosine-induced hyperemia **(C)**. When reached to maximal hyperemic state by administrating incremental dosages of adenosine, the calculated fractional flow reserve (FFR) was found to be 0.57. The distal pressure waveform in **D** (lower waveform) was significantly altered as compared with the baseline proximal signal (upper waveform). This is especially prominent with regard to the absence of the dicrotic notch in the distal waveform, indicating attenuation of the high-frequency components of the pressure waveform across the stenosis and resulting in a pulse transmission coefficient value of 0.32, which suggest, in accordance with the FFR value, a functionally significant lesion. *Continued on next page.*
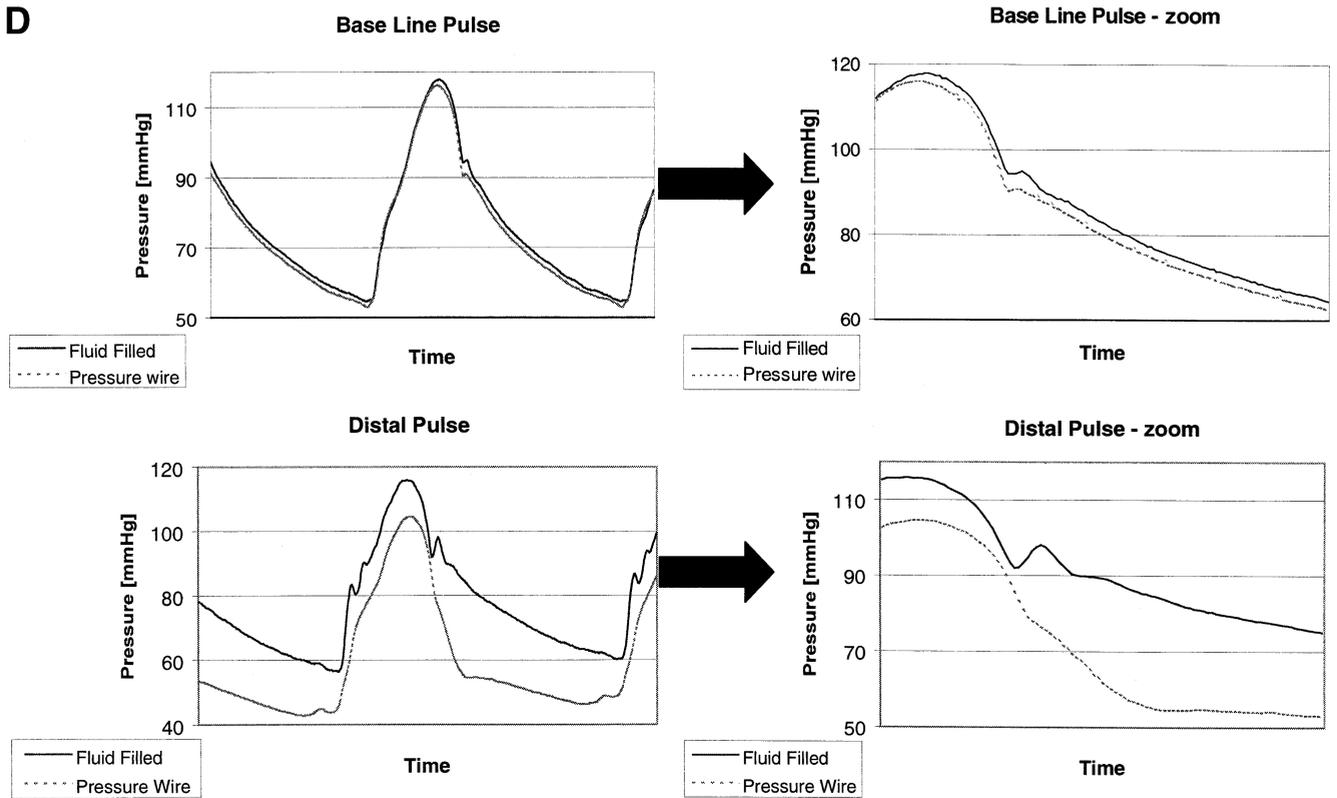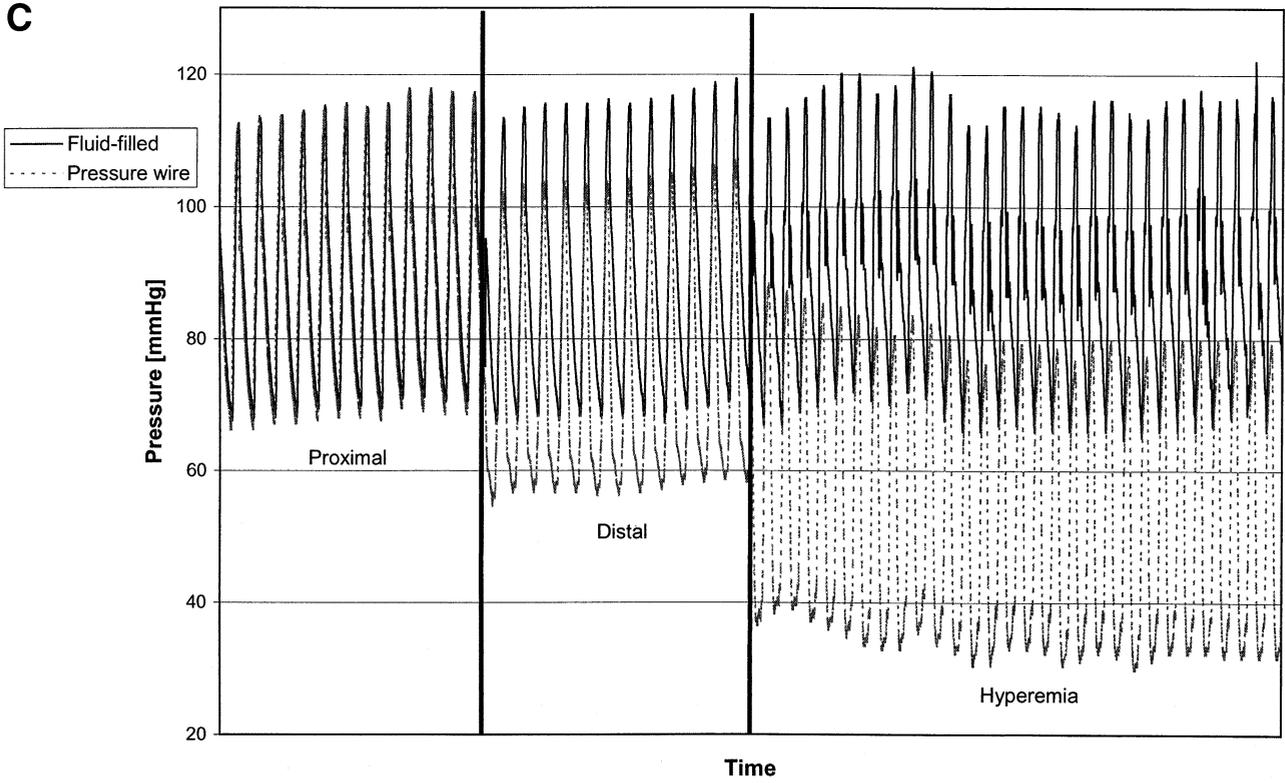
**C**



**D**



**Figure 3.** *Continued from previous page.*

high-frequency components of the pressure waveform across the lesion.

**Physiologic assessment of coronary lesions by FFR.** Although the angiographic assessment of coronary stenosis is the gold standard for assessing coronary disease severity, it has many limitations (17–19), especially when clinical decisions with regard to the need for intervention have to be taken for angiographically intermediate lesions. In such cases, documentation of myocardial ischemia related to the culprit lesion, obtained by functional test, is essential. Therefore, in light of the need for complementary physiologic assessment and with the recent introduction of miniature high-fidelity pressure guidewires FFR has emerged as an important tool for clinical decision-making with regard to the need for intervention.

Fractional flow reserve is derived from intracoronary pressure measurements during maximal hyperemia, induced pharmacologically by vasodilator agents such as adenosine or papaverine, and reflects the fraction of the maximal blood flow across the myocardial bed that can still be obtained in the presence of an epicardial coronary stenosis (20). An FFR value of 0.75 can reliably discriminate between functionally significant lesions, associated with inducible ischemia and nonsignificant lesions (4–6,20–24). Physiologic assessment of coronary lesion by FFR has the advantage of being a lesion-specific index of epicardial conductance, which is almost independent of any hemodynamic changes, induced by variation in heart rate, blood pressure or myocardial contractility during the measurement, and is less affected by microvascular disease as compared with coronary flow reserve (5,15,25,26).

**Clinical and technical limitations of FFR.** Distal pressure depends on flow across the stenosis, which is determined by both epicardial and microvascular resistance. Therefore, FFR has some limitations in certain clinical conditions, such as severe microvascular disease and myocardial infarction remodeling (27), characterized by the development of highly resistant scar tissue in the target artery territory. Both conditions may reduce the maximal achieved epicardial blood flow and may render the FFR value to be overestimated (5,20,28,29). Another clinical condition where FFR assessment might have limitations is in left ventricular hypertrophy, where, as a result of disproportional growth of the vascular bed to the increased myocardial muscle mass, the FFR cutoff value to indicate inducible ischemia is expected to be higher than 0.75 with increasing severity of hypertrophy (25).

In addition, there might be some technical issues that could limit the use of FFR in the evaluation of coronary disease severity. Among them are signal drift during the pressure measurement and difficulties in assessment of ostial lesions, where damping of the pressure signal, either at rest or during maximal hyperemia, by the guiding catheter can lead to a subsequent underestimation of the functional significance of the interrogated lesion (28). Moreover, because maximal hyperemia cannot be reached in 10% to 15% of the patients (28), the reliability of FFR in these cases may be affected. Thus, a nonhyperemic parameter may serve as an adjunct parameter for the assessment of the physiologic significance of CAD.

**Study limitations.** In this present study, the study population consisted of patients that were referred to coronary catheterization mainly based on clinical grounds. Most of those who had clinical presentation of positive ischemia did not undergo further intracoronary physiologic assessment and FFR measurement and, therefore, were not included in the study. This may cause some bias in the patient population and may explain the poor correlation between FFR and PTC and the functional test results.

Another potential limitation is that, although our data suggest a high correlation between PTC and FFR, it seems that a larger variance in FFR was observed for extreme PTC values (0 or 1), whereas there was a relative lack of data points for intermediate PTC values in the range of 0.4 to 0.8 (Fig. 2). A plausible explanation for these findings is that the lesion may act as a mechanical high-frequency filter that is characterized by having a cutoff point of physiologic severity. Only above this threshold point, the lesion sharply attenuates the high-frequency components of the pressure waveform as it crosses the stenosis. Therefore, for most physiologic nonobstructive stenoses with FFR $\geq$0.75, the lesion transmits all frequency components of the pressure waveform and apparently does not function as a filter. This may result in PTC values around 1. On the other hand, for most physiologic obstructive stenoses with FFR $<$0.75, the lesion sharply attenuates all the high-frequency components, resulting in PTC values around 0. Therefore, secondary to this binary behavior of the lesion as a high-frequency filter, there are relatively few data points in the PTC range of 0.4 to 0.8, as compared with the two ends of the spectrum (PTC = 0 or 1). This, however, may potentially lower the reliability of the sensitivity and specificity as well as the correlation with FFR at higher values of PTC, where it may be particularly relevant for the physiologic lesion assessment after percutaneous coronary interventions.

The present study demonstrates that this nonhyperemic parameter correlates with FFR and can be easily applied as an adjunct index to FFR for the physiologic assessment of CAD.

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## APPENDIX

The algorithm steps are outlined below:

1. The measured pressure signal, $P(t)$, is filtered by using a low pass filter. The resulted filtered signal, $P_{low}(t)$, contains only the first six harmonics of the initial $P(t)$ signal. The signals $P(t)$ and $P_{low}(t)$ are shown in Figure 1A by solid and dotted lines, respectively.

2. The difference between measured and filtered pressure signals is calculated: $\Delta P(t) = P(t) - P_{low}(t)$. The function $\Delta P(t)$ is depicted at the bottom of Figure 1B, and the measured pressure signal $P(t)$ is depicted above it.

3. The high-frequency components of the pressure signal are observed at the points of maximum and minimum pressure and at the dicrotic notch region. Hence, the region of interest (ROI) is defined by zero values of the function $\Delta P(t)$ adjacent to the minimum of the function. The ROI is depicted in Figure 1B by a dotted rectangle.

4. The standard deviation (E) of the function $\Delta P(t)$ is calculated within the ROI, where $E = std_{ROI}[\Delta P(t)]$. This standard deviation represents the difference in filtered versus unfiltered signals within the ROI. The function E is calculated at proximal and distal locations across the lesion, and the $PTC = E_{distal}/E_{proximal}$.