

# Nonhyperemic Intracoronary Pressure Waveform Analysis Predicts the Fractional Flow Reserve

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## Abstract

The fractional flow reserve (FFR) is measured during maximal hyperemia achieved by intracoronary or intravenous vasodilator. It has been regarded that the nonhyperemic resting pressure ratio (RPR) was not appropriate for exact evaluation of the functional severity of coronary lesion. Some studies suggest, however, that the comparison of the proximal and distal resting waveform of the stenosis may predict the fractional flow reserve (FFR), because the intracoronary waveform has such a high-frequency pressure signal at the closing of aortic valve (notch) that can be decreased by the filter-effect of the stenosis.

In our investigation we analyzed the derivatives of the pre- and post-stenotic basal pressure waves of 40 pressure measurements, and the resting pressure ratio (RPR). These data were compared to the measured FFR values during hyperemia. We introduced the delta  $\delta p_N/dt$  value ( $\delta p_N/dt$ ) to characterize (describe?) the ascending slope of the dicrotic notch. This is the difference between the local minimum and maximum values of the derivatives of the pressure waveform during the dicrotic notch period. We have experienced significant correlation between the  $\delta p_N/dt$  and FFR ( $r= 0.59$ ,  $p < 0.001$ ) as well as the RPR and the ( $r= 0.65$ ,  $p= 0.004$ ) FFR. By using the Receiver Operating Curve (ROC) analysis, the value of  $3 > \delta p_N/dt$  (sensitivity 100%, specificity 91%), and an  $RPR > 0.87$  (sensitivity 88%, specificity 84%) were found to be the optimal cutoff values for predicting  $FFR < 0.75$ . The areas under the ROC were 0.99 in case of  $\delta p_N/dt$  and 0.92 in case of RPR.

The  $\delta p_N/dt$  can be a new useful nonhyperemic parameter for the assessment of the coronary artery stenosis during the intracoronary pressure measurements.

## 1. Introduction

Coronary angiography currently is the gold standard for assessing coronary artery disease (CAD). However the functional severity of intermedier stenoses (40-70%

narrowing in diameter) cannot be evaluated by this modality, therefore proper clinical decision-making would require an additional diagnostic procedure. The determination of the fractional flow reserve (FFR) by pressure sensor guidewire has become the gold standard for the functional assessment because FFR has been showed good correlation with the degree of myocardial ischemia and coronary events. During coronary catheterization maximal hyperemia is pharmacologically stimulated (often with intracoronary adenosine), and both Pa (aortic pressure at the guide tip) and distal coronary pressure (Pd, at the pressure sensor) are simultaneously measured. FFR is calculated as  $Pa/Pd$ , and a value  $< 0.75$  implies significance, with values between 0.75 and 0.80 considered a “gray zone.” In studies this value strongly correlates with noninvasive ischemia, and post-intervention resolution of abnormal FFR also correlates with resolution of ischemia. Furthermore, there are 5-year prospective and retrospective data clearly demonstrating that interventions on intermediate lesions with  $FFR \geq 0.75-0.80$  can be safely deferred with an annual risk of cardiac death or myocardial infarction  $< 1\%$  (DEFER and FAME study) (1-5)

It has been regarded that the nonhyperemic resting pressure ratio (RPR) was not appropriate for exact evaluation of the functional severity of coronary lesion. Some studies suggest, however, that the comparison of the proximal and distal resting waveform of the stenosis may predict the fractional flow reserve (FFR), because the intracoronary waveform has such a high-frequency pressure signal at the closing of aortic valve (notch) that can be decreased by the filter-effect of the stenosis (6). In our work an attempt has been made to identify a nonhyperemic parameter correlating directly with the severity of coronary artery stenosis by deriving the resting pressure waveforms.

## 2. Methods

We studied 22 patients with coronary artery disease and without significant aortic valve disease (19 men, 3 women; age:  $61 \pm 10.2$  years). On 31 stenosed vessels (15 LAD, 2 LCx, 11 RCA, 2 I. diagonal, 1 OM) 40 pressure

measurements (9 times after PCI) were carried out by PressureWire Certus (Radi Medical). The pressure curves were exported through the RadiView software to a JAVA program developed by our team, and the dp/dt were calculated (dt=1/100 sec). In order to characterize the ascending slope of the dicrotic notch, the difference between the local minimum and maximum values of the derivative of the pressure wave during the dicrotic period ( $\delta dp_N/dt$ ) was calculated as follows:

$$\delta dp_N/dt = dp_N/dt_{\min} - dp_N/dt_{\max}$$

where

$dp_N/dt_{\min}$ : the value of the dp/dt curve of the distal intracoronary pressure trace at the beginning of the dicrotic notch (the green trace on the second rows on **figure 1**.)

$dp_N/dt_{\max}$ : the first local peak of the dp/dt curve of the distal intracoronary pressure trace during the dicrotic notch

Given that in cases without significant aortic stenosis the dp/dt of the proximal pressure trace always has a clear minimum value at the time of the closure of the aortic valve, the identification of the beginning of the dicrotic notch on the distal dp/dt is easy, even in case of very blunted dicrotic notch on the distal pressure trace. After the identified beginning of the dicrotic notch of the distal dp/dt curve on **figure 1/A** there is a further decrease in the dp/dt during the dicrotic notch period in association of the rapid decrease of the original distal pressure trace in this period. This patient had a functionally very tight lesion with a high resting translesional gradient and with an FFR of 0.42. In this case the value can be calculated to be -1.9. All the other cases we had positive values ranged up to 12. On the **B** panel of **figure 1**. the traces were recorded after the stent implantation. On the **B** panel the  $\delta dp_N/dt$  increased to 5.8 parallel with the normalization of the resting distal trace (upper row of B panel) and the elimination of the resting gradient.

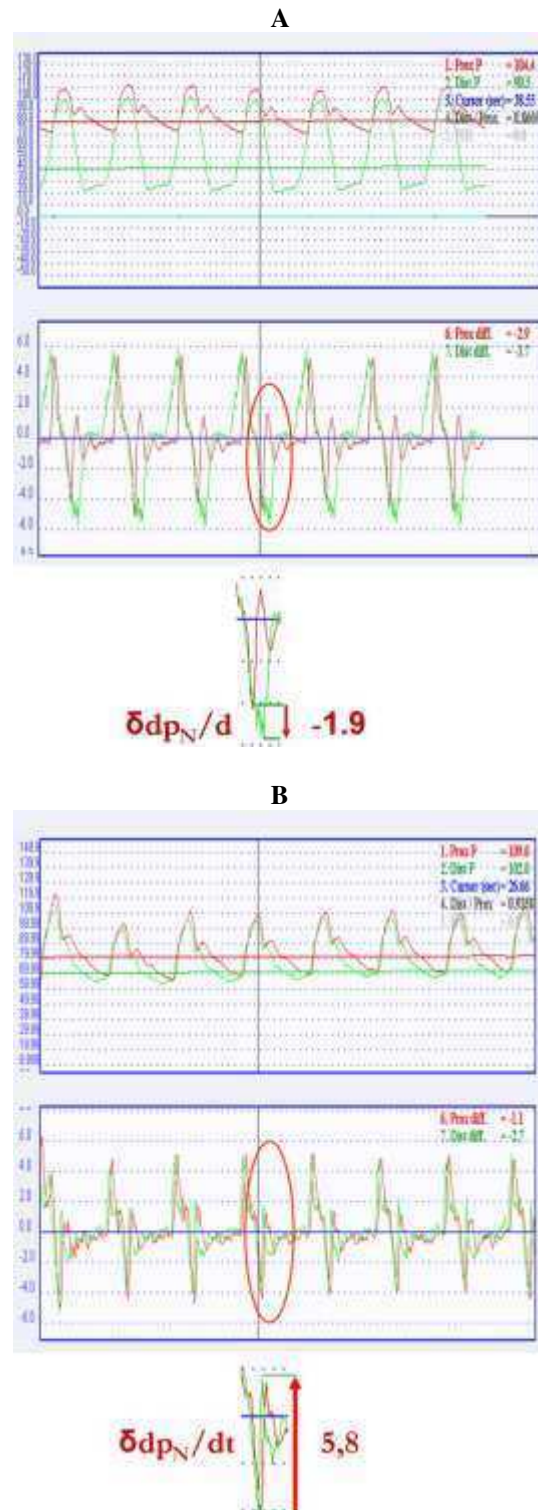


Figure 1. The pressure waveforms (first rows) and their derivatives (second rows) before (A) and after stenting (B). The red curves (represent? are) the proximal (aortic) traces, while the green curves (represent? are) the distal intracoronary traces. The third row shows the calculation of the  $\delta dp_N/dt$  (see details in the text).

### 3. Results

There was a significant correlation between the  $\delta dp_N/dt$  and the FFR (figure 2.), as well as the RPR and the FFR ( $r= 0.59$ ,  $p < 0.001$  and  $r= 0.65$ ,  $p= 0.004$ , respectively) (figure 3.). By using the Receiver Operating Curve (ROC) analysis, the value of  $3 \geq \delta dp_N/dt$  (sensitivity 100%, specificity 91%), and an **RPR=0.87** (sensitivity 88%, specificity 84%), was found to be the optimal cutoff values for predicting  $FFR \leq 0.75$ . The area under the ROC was 0.99 in case of  $\delta dp_N/dt$  and 0.92 in case of RPR (figure 4.).

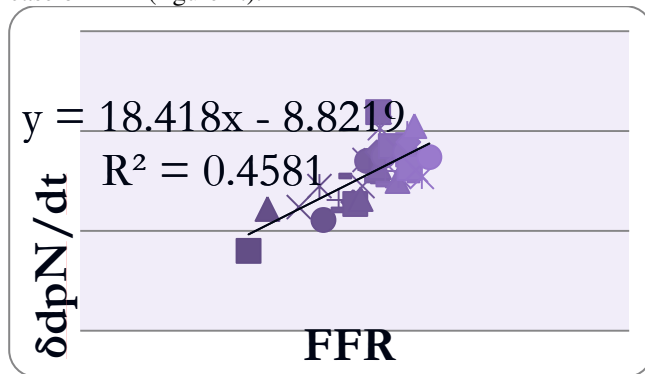


Figure 2. Correlation between  $\delta dp_N/dt$  and FFR

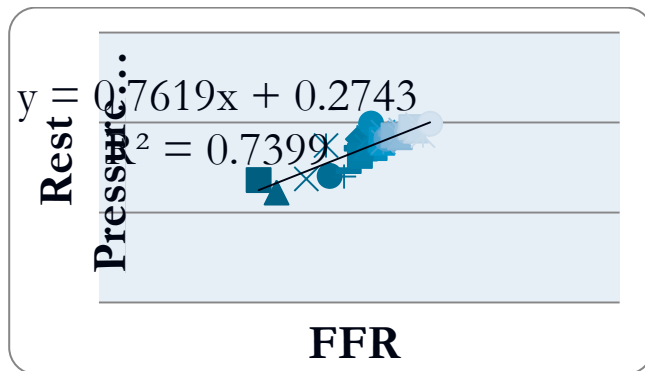


Figure 3. Correlation between RPR and FFR

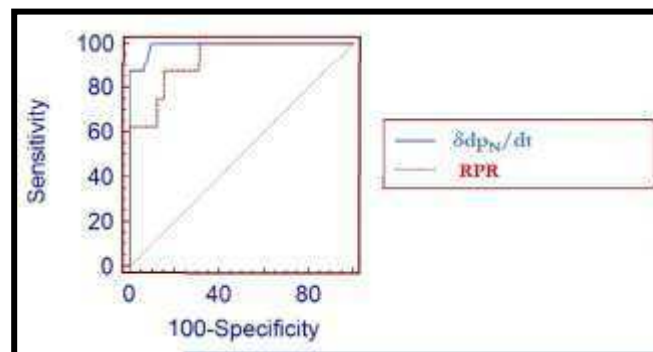


Figure 4. ROC analysis of the  $\delta dp_N/dt$  and the RPR for  $FFR \leq 0.75$ .

### 4. Discussion and conclusions

Despite FFR is a fairly simple method for the assessment of the flow limitation of a coronary lesion, it requires to achieve maximal hyperemia which can be time-consuming and uncertain. Without hyperemia, the RPR alone is not considered an adequate marker of the functional severity of coronary lesion, because under the basal flow condition there can be no relevant pressure drop on a stenosis despite significant flow limitation and gradient during hyperemia. We have found, however, a weak correlation between the RPR and the FFR in our patient population. This result is in line with other's data (7), and can be explained by the fact that very severe stenosis can cause resting gradient, too. On the other hand, the variable increase of flow, depending also on the myocardial microvasculature, may result in variable translesional gradient on the same degree stenosis during hyperemia. Consequently, it is feasible to find a more reliable nonhyperemic parameter. Brosh et al. proposed the calculation of the pulse transmission coefficient for this purpose (6). According to their concept, spectral analysis of the pressure waveform shows that at the closing of aortic valve the aortic valve segment contains high-frequency component, therefore this region is appropriate for analyzing the changes in the high-frequency content of the pressure signal. The pulse transmission coefficient was the ratio between the distal and proximal high-frequency component of the pressure waveform across the lesion. They found that the lesion may act as a mechanical high-frequency filter that is characterized by having a cutoff point of physiologic severity.

Our approach is also based on the waveform analysis of the resting pressure trace. In our opinion, there is an easier way to quantify the blunting of the aortic valve notch than using the previously described method. Our proposed parameter, the  $\delta dp_N/dt$  can be a new useful nonhyperemic value for the assessment of the coronary artery stenosis during the intracoronary pressure measurements. The software developed by our team is appropriate for on-line evaluation of the resting pressure wave, which can provide direct guidance for decision making on intermediate coronary lesions. It can also provide immediate assessment of the effect of stent implantation.

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