Analysis of pulsatile coronary pressure and flow velocity: looking beyond means
Kolyva, C.

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Chapter 3

Hyperemic stenosis resistance and intramyocardial pump function assessed from phasic energy of coronary flow velocity and pressure signals

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Submitted
Abstract

**Background:** A novel measure of strength of pulsatility of coronary flow velocity, \( v \), aortic pressure, \( P_a \), and distal pressure, \( P_d \), were used 1) to test hypotheses explaining pulsatility of \( v \) and \( P_d \) and 2) to quantify the physiological significance of a coronary stenosis without pharmacological vasodilatation.

**Methods:** Pulsatile indices for \( P_a \), \( P_d \) and \( v \), denoted as PPI\( _a \), PPI\( _d \) and PvI, were derived in target vessels (29 patients) and reference vessels (subgroup of 23 patients). Stenosis resistance, SR, was defined as \( (P_a - P_d)/v \), pulsatile stenosis resistance index, PRI, as abs(PPI\( _d \) – PPI\( _a \))/PvI and microvascular conductance, MC, as \( v/P_d \).

**Results:** PvI correlated well with MC at rest in the reference vessel (baseline and hyperemia) and target vessel (baseline) with \( r \)'s ranging from 0.62 – 0.79 and \( P<0.005 \). In the target vessel during hyperemia the correlation was still significant \( (P<0.05) \) before but not after stent placement. PvI did not correlate with beat-averaged \( P_d \) or PPI\( _d \) for any of these conditions.

Hyperemic SR correlated very well with SR at rest \( (r = 0.96, P<0.0001) \) and was also predicted rather well by PRI. The relation between PRI and hyperemic SR for the left \( (r = 0.93, P<0.0001) \) was different for the one at right \( (r = 0.97, P<0.005) \) target vessel.

**Conclusions:** Our data are consistent with the intramyocardial pump model, but do not support the elastance hypothesis as explanation for coronary flow pulsations. PRI defines the physiological significance of a stenosis without the need for hyperemia and is not affected by drift in the pressure transducer.
Introduction

In contrast to the time-averaged means of coronary flow and pressure, the pulsatile nature of these signals is much less exploited to study human coronary physiology in normal and diseased coronary arteries. Animal studies allow employment of a constant pressure or flow perfusion system so that the phasic characteristics are restricted to one of these two signals only, thereby facilitating the interpretation of the effects of cardiac contraction on coronary perfusion [9]. However, this approach is hardly possible in the clinical setting during coronary catheterization in humans.

In this study we propose a simplified method for quantifying the pulsatility of coronary signals via the concept of signal energy applied to coronary pressure and flow velocity. In signal processing, the average energy of the pulsatile component of a signal is obtained by first subtracting the mean of the signal, which renders the average of the remaining signal zero, and then raising this signal to the power of two. What remains is a purely positive signal and the integral per beat is known as the energy of the pulsatile component [13]. The square root of this signal has the same physical units as the original signal and is referred to in this paper as the Pulsatile Index signal. The interaction between pulsatile indices of pressure and flow velocity can then be interpreted analogous to respective signal amplitudes in perfusion-controlled animal studies, but without specific demands on the shape of either signal.

The pulsatile nature of coronary pressure and flow arises from the contraction of the cardiac muscle and hence the pulsatile signal content could reveal information on the underlying mechanism of the intramyocardial pump, IMP, action [7, 21]. The driving force for this IMP was assumed to be tissue pressure related to left ventricular pressure [16]. Some years later, findings obtained from perfusion-controlled isolated heart experiments suggested that flow pulsatility was dominated by myocardial elastance variations throughout the heart beat [10, 11]. The data were interpreted based on the assumption that hyperemic microvascular resistance was independent of perfusion pressure. However, the pressure-dependence of microvascular resistance at full dilation has been demonstrated in animals [6] and recently confirmed in humans [20]. Therefore we hypothesized that an attenuation of pulsatility in flow at a lower perfusion pressure may be caused by an increased hyperemic coronary microvascular resistance rather than a decreased elastance effect.

The phasic characteristics of coronary pressure and flow velocity also change in the presence of a stenosis [3] and we hypothesized that this change is related to hyperemic stenosis resistance (HSR), which was shown earlier to be an excellent predictor of inducible ischemia [12]. We therefore defined a pulsatile stenosis resistance index, PRI, as the ratio of the difference between pulsatile indices of distal coronary and aortic pressure and of distal coronary flow velocity and correlated PRI with HSR. We did so since the application of PRI would have advantages over existing indices of the physiological significance of a stenosis since PRI is insensitive to drift of the pressure transducer and does not require pharmacological vasodilatation.
Methods

Study population
Twenty-nine patients (23 males) with stable angina pectoris scheduled for elective balloon angioplasty participated in this study. All patients had at least one angiographically normal vessel (<30% diameter stenosis) and one stenotic vessel with a single de novo lesion scheduled for angioplasty. Exclusion criteria for this study included diffuse or 3-vessel disease, significant left main coronary artery stenosis, subtotal lesions, hypertrophic cardiomyopathy, recent myocardial infarction (<6 weeks) or prior cardiac surgery. The protocol was approved by the Medical Ethics Committee of our institute and all patients gave informed written consent.

Medication and protocol
Antianginal and antiplatelet medication was continued as prescribed. The patients received Lorazepam (1 mg, orally) before cardiac catheterization. After heparinization (7500 IU) nitroglycerine (0.1 mg, i.c.) was given to relax smooth muscle tone in the epicardial vessels. Transient maximal hyperemia was induced with an intracoronary bolus (20-40 μg) of adenosine.

Hemodynamic data were acquired first in an angiographically normal vessel (reference vessel) and then in the stenotic vessel (target vessel) before and after stent placement. Data for each of these three conditions were collected continuously at rest and throughout the build-up and decline of maximal hyperemia.

Aortic pressure, $P_a(t)$, was obtained via a 5 or 6F guiding catheter that was advanced into the coronary ostium from the right femoral artery. Distal intracoronary perfusion pressure, $P_d(t)$, and flow velocity, $v(t)$, were measured simultaneously with a dual-sensor guidewire (diameter 0.35 mm, Volcano Corp., Rancho Cordova, CA) equipped with a Doppler sensor at the tip and a pressure sensor 3 cm proximal to the tip [14]. The outputs of the two sensors were sent to their corresponding consoles (WaveMap and FloMap, Volcano Corp.) for processing. All hemodynamic signals and the ECG were recorded on a personal computer for off-line analysis, after digitization at a sampling rate of 120Hz.

Prior to angioplasty, $P_d(t)$ and $v(t)$ in the target vessel were measured distal to the stenosis (condition denoted as pre) and at approximately the same location after angioplasty (denoted as stent). The position of the guidewire tip was checked with short angiographic sequences. Similarly, a distal measuring location was selected in the reference vessel (noted as ref). At all locations, the wire tip was manipulated until an optimum and stable flow signal was obtained.

Data analysis
Data analysis was performed using custom software (written in Delphi, version 6.0, Borland Software Corporation, Cupertino, CA). For each of the three steps of the protocol, a number of consecutive beats (2-3 for hyperemia, 8-9 at baseline) representative of resting and hyperemic conditions were selected.

Based on this selection, mean baseline and hyperemic values for aortic pressure, $P_a$, distal coronary pressure, $P_d$, and flow velocity, $v$, and HR were calculated. We note that throughout this paper, the expression $y(t)$ is used to refer to a time-varying signal,
while the symbol $y$ refers to its mean value. Velocity-based indices of mean microvascular resistance and stenosis resistance were derived as $MR = \frac{P_d}{v}$ and $SR = \frac{(P_a - P_d)}{v}$, respectively [12, 14, 20].

From the same selections of signals, the respective pulsatile indices of aortic and distal pressure and flow velocity were derived as [13]:

$$PPI_a = \sqrt{\frac{1}{n} \sum (P_a(t) - \overline{P_a})^2} \quad (3.1)$$

$$PPI_d = \sqrt{\frac{1}{n} \sum (P_d(t) - \overline{P_d})^2} \quad (3.2)$$

$$PvI = \sqrt{\frac{1}{n} \sum (v(t) - \overline{v})^2} \quad (3.3)$$

The summation was taken over complete heart cycles and then divided by the total number of samples, $n$, in order to render these quantities independent of the number of sampling points included in each selection. The pulsatile aortic pressure index, $PPI_a$, and pulsatile coronary pressure index, $PPI_d$, and pulsatile velocity index, $PvI$, were then derived as the square root of the respective energies.

The pulsatile resistance index of stenosis severity was derived from these indices as

$$PRI = \frac{|PPI_d - PPI_a|}{PvI} \quad (3.4)$$

In the absence of left ventricular pressure measurement, an index of cardiac contractility was calculated from the ratio of $P_a(t)$ at the time of opening of the aortic valve divided by the time interval from the beginning of the cycle until the aortic valve opening. This index gives an indication of the rate of pressure build-up in the left ventricle.

**Statistical analysis**

Data are expressed as mean ± SEM. Hemodynamic data obtained for different steps of the protocol were compared using ANOVA with repeated measures followed by contrast analysis (SPSS, version 12.0). Results for resting and hyperemic conditions at the same step of the protocol were compared using paired t-tests. Possible relations between different parameters were evaluated using linear regression analysis. Statistical significance was assumed at $P<0.05$.

**Results**

The mean age of the patients was 59 ± 2 years. Vessel characteristics are summarized in Table 3.1. Reference vessel measurements were not available in 6 patients. Percent diameter stenosis varied between 27% and 76%, with a mean of 55.7 ± 2.2%. The majority of the studied vessels were main branches of the left coronary artery and 21% of the target vessels were right coronary vessels.
Table 3.1: Clinical characteristics.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>59 ± 2</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (m/f)</strong></td>
<td>23/6</td>
<td></td>
</tr>
<tr>
<td><strong>Diameter stenosis, mean (%)</strong></td>
<td>55.7 ± 2.2</td>
<td></td>
</tr>
<tr>
<td><strong>Reference vessel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/LCx/RCA (n) (%)</td>
<td>2/19/2</td>
<td>9/82/9</td>
</tr>
<tr>
<td><strong>Target vessel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/LCx/RCA (n) (%)</td>
<td>19/4/6</td>
<td>65/14/21</td>
</tr>
</tbody>
</table>

LAD: Left anterior descending artery; LCx: Left circumflex artery; RCA: Right coronary artery.

Hemodynamic parameters

Heart rate, contractility and aortic pressure remained essentially constant throughout the protocol (Table 3.2). Distal vasodilation caused an increase in flow velocity and a decrease in $P_d$ ($P<0.0001$), with a 5 mm Hg reduction in $P_a$ ($P<0.0005$). Both $P_d$ and velocity increased after stent placement ($P<0.05$), concomitant with a decrease in stenosis resistance ($P<0.001$) and hyperemic MR ($P<0.005$).

Table 3.2: Mean hemodynamic values.

<table>
<thead>
<tr>
<th></th>
<th>stenosis (n = 29)</th>
<th>stent (n = 29)</th>
<th>reference (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71 ± 2</td>
<td>71 ± 3</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>$P_a$ (mm Hg)</td>
<td>103 ± 3</td>
<td>104 ± 3</td>
<td>103 ± 3</td>
</tr>
<tr>
<td>$P_d$ (mm Hg)</td>
<td>82 ± 4</td>
<td>101 ± 3†</td>
<td>100 ± 3</td>
</tr>
<tr>
<td>$v$ (cm/s)</td>
<td>16.0 ± 1.3</td>
<td>19.0 ± 1.1†</td>
<td>19.6 ± 1.6</td>
</tr>
<tr>
<td>SR (mm Hg/cm/s)</td>
<td>1.75 ± 0.40</td>
<td>0.18 ± 0.03†</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td>MR (mm Hg/cm/s)</td>
<td>5.90 ± 0.50</td>
<td>5.93 ± 0.44</td>
<td>5.79 ± 0.42</td>
</tr>
<tr>
<td>Contractility (mm Hg/s)</td>
<td>1151 ± 62</td>
<td>1096 ± 62</td>
<td>1238 ± 70</td>
</tr>
</tbody>
</table>

| **Hyperemia**            |                  |                |                   |
| HR (bpm)                 | 71 ± 2           | 70 ± 2         | 68 ± 3            |
| $P_a$ (mm Hg)            | 99 ± 3*          | 97 ± 3*        | 97 ± 3*           |
| $P_d$ (mm Hg)            | 61 ± 3*          | 87 ± 3†        | 94 ± 3†           |
| $v$ (cm/s)               | 30.1 ± 2.9*      | 58.1 ± 3.1†    | 54.9 ± 3.5*       |
| SR (mm Hg/cm/s)          | 1.99 ± 0.39†     | 0.19 ± 0.04†   | 0.06 ± 0.01†      |
| MR (mm Hg/cm/s)          | 2.53 ± 0.23*     | 1.67 ± 0.13†   | 1.82 ± 0.09†      |
| Contractility (mm Hg/s)  | 1328 ± 99*       | 1178 ± 78      | 1315 ± 59         |

HR, heart rate; $P_a$, aortic pressure; $P_d$, coronary pressure; $v$, flow velocity; SR, stenosis resistance; MR, microvascular resistance.

*P<0.05 compared to rest; †P<0.05 compared to previous step.

Pulsatile waveforms

The effects of vasodilation on the phasic characteristics of coronary pressure and flow velocity are illustrated in Figure 3.1 before and after PCI of a 68% diameter stenosis in the left anterior descending artery of a 52 yr old male patient. The velocity waveform became more pulsatile during hyperemia compared to rest. This was more pronounced after stent placement (Figure 3.1B), as reflected by the increased energy...
of the velocity signal, shown here by an instantaneous representation of the pulsatile velocity index, \( \text{PvI}(t) \) (third panel in Figure 3.1A and 3.1B).

![Graphs showing coronary hemodynamic signals during resting (left) and hyperemic (right) conditions before (A) and after revascularization (B) of a 68% diameter stenosis in the left anterior descending artery. With a stenosis, amplitude variations in distal pressure increased during hyperemia, resulting in marked differences in aortic and distal PPI. After stent placement with 8% residual stenosis, the pulsatility in velocity increased substantially.

\( v \), flow velocity; \( P_a \), aortic pressure; \( P_d \), distal coronary pressure; \( \text{PvI} \), pulsatile velocity index; \( \text{PPI} \), pulsatile pressure index.]

Figure 3.1: Coronary hemodynamic signals during resting (left) and hyperemic (right) conditions before (A) and after revascularization (B) of a 68% diameter stenosis in the left anterior descending artery. With a stenosis, amplitude variations in distal pressure increased during hyperemia, resulting in marked differences in aortic and distal PPI. After stent placement with 8% residual stenosis, the pulsatility in velocity increased substantially. \( v \), flow velocity; \( P_a \), aortic pressure; \( P_d \), distal coronary pressure; \( \text{PvI} \), pulsatile velocity index; \( \text{PPI} \), pulsatile pressure index.
The pulsatile amplitude of the distal pressure waveform during hyperemia displayed the typical enhancement induced by a stenosis (Figure 3.1A, right). Owing to the higher velocity in diastole, differences between $P_a$ and $P_d$ were largest in this phase of the cardiac cycle, which is also noticeable from the instantaneous variations of the corresponding pulsatile pressure indices, PPI(t) (bottom panels in Figure 3.1A and 3.1B). The signals obtained from the reference vessel (not shown) resembled those of the target vessel after stent placement, with a small effect of vasodilation on distal pressure.

**Pulsatile pressure and velocity indices**

The pulsatile index of aortic pressure (PPI$_a$) remained essentially constant under all conditions, while that of stenosis resistance (PRI) significantly decreased after stent placement ($P<0.0005$) (Table 3.3). Changes in PPI$_a$ and PVI are depicted in Figure 3.2A and B, respectively, as a function of average distal pressure. In the presence of a stenosis, PVI increased by only a factor of 1.3 (from 5.8 to 7.7 cm/s, $P<0.01$) with vasodilatation. PPI$_a$ remained approximately constant at about 23 mm Hg, although $P_d$ dropped from 82 to 61 mm Hg ($P<0.0001$). In contrast, PVI increased from 7.7 to 17.4 cm/s ($P<0.0001$) during hyperemia after PCI, and PPI$_a$ from 19.1 to 21.7 mm Hg ($P<0.0001$). Similarly, PVI increased with vasodilation by a factor of 2.3 (from 8.5 to 19.7 cm/s) ($P<0.0001$) in the reference vessel, but PPI$_a$ hardly changed ($P<0.05$).

Stent placement restored PVI to reference values during baseline ($P<0.01$) and hyperemia ($P<0.0001$), but only had a significant influence on PPI$_a$ at rest ($P<0.05$).

**Table 3.3. Pulsatile indices.**

<table>
<thead>
<tr>
<th></th>
<th>stenosis (n = 29)</th>
<th>stent (n = 29)</th>
<th>reference (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$PPI_a$ (mm Hg)</td>
<td>18.5 ± 1.5</td>
<td>18.3 ± 1.6</td>
<td>19.3 ± 1.6</td>
</tr>
<tr>
<td>$PPI_d$ (mm Hg)</td>
<td>22.4 ± 1.6</td>
<td>19.1 ± 1.5†</td>
<td>19.7 ± 1.6</td>
</tr>
<tr>
<td>PVI (cm/s)</td>
<td>5.8 ± 0.5</td>
<td>7.7 ± 0.6†</td>
<td>8.5 ± 1.0</td>
</tr>
<tr>
<td>PRI (mm Hg s/cm)</td>
<td>2.5 ± 0.3</td>
<td>0.9 ± 0.1†</td>
<td>0.5 ± 0.1†</td>
</tr>
<tr>
<td><strong>Hyperemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$PPI_a$ (mm Hg)</td>
<td>19.4 ± 1.5*</td>
<td>19.6 ± 1.5*</td>
<td>19.9 ± 1.5</td>
</tr>
<tr>
<td>$PPI_d$ (mm Hg)</td>
<td>23.6 ± 1.2</td>
<td>21.7 ± 1.4*</td>
<td>20.4 ± 1.5*</td>
</tr>
<tr>
<td>PVI (cm/s)</td>
<td>7.7 ± 0.8†</td>
<td>17.4 ± 1.2†</td>
<td>19.7 ± 1.7*</td>
</tr>
<tr>
<td>PRI (mm Hg s/cm)</td>
<td>2.8 ± 0.3</td>
<td>0.9 ± 0.2†</td>
<td>0.2 ± 0.03†</td>
</tr>
</tbody>
</table>

PPI$_a$, aortic pulsatile pressure index; PPI$_d$, coronary pulsatile pressure index; PVI, pulsatile velocity index; PRI, pulsatile resistance index.

* $P<0.05$ compared to rest; † $P<0.05$ compared to previous step.
Figure 3.2: (A) Distal pulsatile pressure index versus mean coronary pressure. Vasodilation caused a significant increase in PPI₅₀ both after stent placement and in the reference vessel. (B) Pulsatile velocity index as a function of beat-averaged coronary pressure.

Determinants of pulsatile velocity index

Pvi increased with coronary microvascular conductance (MC = 1/MR) both at rest and hyperemia (Figure 3.3) in all vascular conditions. The dependence of Pvi on MC was stronger in the reference vessel than in the target vessel either before or after stent placement. Multiple linear regression on the combined influence of MC and stenosis resistance, SR, on Pvi revealed a significant additional contribution of SR only in the stented vessel during hyperemia ($r = 0.56$, $P<0.01$). There was no significant correlation between PPI₅₀ and MC.
Figure 3.3: Positive correlations between pulsatile velocity index and microvascular conductance at rest (A) and hyperemia (B). Rest: $r = 0.63$, $P<0.0005$ (stenosis); $r = 0.70$, $P<0.0001$ (stent); $r = 0.79$, $P<0.0001$ (reference). Hyperemia: $r = 0.45$, $P<0.05$ (stenosis); $r = 0.32$, $P = 0.09$ (stent); $r = 0.62$, $P<0.005$ (reference).

Although hyperemic PVI was weakly related ($r = 0.4$, $P = 0.03$) to coronary pressure, $P_d$, in the diseased vessel (Figure 3.4), a significant relationship between these two parameters was not maintained after stent placement or in the reference vessel. No significant correlation existed between PVI and mean aortic pressure or aortic pulsatile pressure index, $PPI_a$. 
Figure 3.4: Absence of correlation between hyperemic pulsatile velocity index, \(PvI\), and distal coronary pressure, \(P_d\). \(r = 0.40, P = 0.03\) (stenosis); \(r = 0.18, P = 0.35\) (stent); \(r = 0.08, P = 0.72\) (reference). Closed circles: stenosis; open circles: stent; triangles: reference.

**Mean stenosis resistance and pulsatile resistance index**

There was an excellent correlation between baseline and hyperemic stenosis resistance for both the left and right diseased vessels as shown in Figure 3.5: \(SR_{hyp} = 0.93 \times SR_{rest} + 0.37\) (\(n = 29, r = 0.96, P<0.0001\)). Note that the relation is not going through the origin and the slope is less than one.

Figure 3.5: Excellent linear relationship between stenosis resistance at hyperemia and at rest. \(r = 0.96, P<0.0001\).

PRI is based on the difference between the pulsatile pressure indices \(PPI_d\) and on \(PvI\) (Eq. 3.4) and the dependence of these indices on hyperemic SR is depicted in
Figure 3.6A and B, respectively. PVI did not correlate with hyperemic SR in either left (r = 0.287) or right (r = 0.330) target vessels. The absolute value of \((PPI_d - PPI_a)\) correlated nicely with hyperemic stenosis resistance, with different relationships for the left (r = 0.826) and right coronary arteries (r = 0.918). A strong linear relationship was found between mean stenosis resistance at hyperemia and PRI at rest (Figure 3.7). These relations were distinctly different for the left \(SR_{hyp} = 1.85 \times PRI_{rest} - 0.04\) \((n = 23, r = 0.93, P<0.0001)\) and right target vessels \(SR_{hyp} = 3.92 \times PRI_{rest} + 0.45\) \((n = 6, r = 0.97, P<0.001)\). Even when all vessels were grouped together the correlation between PRI at rest and hyperemic SR was rather good, \(SR_{hyp} = 1.85 \times PRI_{rest} + 0.30\) \((n = 29, r = 0.85, P<0.0001)\).

Figure 3.6: (A) Significant correlations between \(\text{abs}(PPI_d - PPI_a)\) and stenosis resistance for right coronary artery (closed symbols, \(r = 0.918\)) and left coronary artery (open symbols, \(r = 0.826\)). (B) Absence of correlation between PVI and stenosis resistance for right coronary artery (closed symbols, \(r = 0.330\)) and left coronary artery (open symbols, \(r = 0.287\)).
Discussion

Based on pulsatile indices of aortic and coronary pressure and flow velocity obtained at rest, a pulsatile index of stenosis resistance, PRI, has been derived that correlates highly with coronary stenosis resistance measured at hyperemia. This relationship is different for the right and left coronary arteries. Since hyperemic SR is a good predictor of inducible ischemia as determined by SPECT [12], PRI has the potential of becoming such a predictive index as well, with the additional advantage of being based on measurements at rest and not being sensitive to pressure-transducer-related drift. Furthermore, we found that the pulsatile velocity index, PvI, was strongly related to microvascular conductance, MC, but not to distal coronary pressure as predicted by the elastance model [11]. Our findings demonstrate a dominant role for coronary microvascular resistance in damping coronary flow pulsations both at rest and during hyperemia.

Physiological interpretation of coronary pulsatile velocity index, PvI

The intramyocardial pump model [16] assumes that the compression of the coronary microvessels displaces blood out of the intramural vessels into both arteries and veins, inducing a decrease in arterial systolic flow that in some circumstances may become negative and an increase in venous systolic flow. Consequently, the systolic-diastolic variations in arterial blood flow that are superimposed on its mean value are attributed to corresponding changes in intramyocardial blood volume. Therefore, the pulsatility of coronary flow depends on the force by which intramural blood volume is displaced and on the impediment of flow variations by resistance vessels.

Originally it was assumed that the intramural vessels were compressed via transmission of left ventricular pressure, $P_{LV}$, to tissue pressure. This hypothesis corresponded with the dominant effect of myocardial contraction on subendocardial flow [2]. However, later...
studies demonstrated that coronary flow was still pulsatile in the empty beating heart and hence $P_LV = 0$ [10]. In this condition subendocardial perfusion was still lower than epicardial perfusion [19]. These observations resulted in the elastance hypothesis where it is assumed that at the same elastance variations during systole, intramural pressure pulsations and consequently coronary arterial flow variations are larger when the intramural vascular volume is filled to a higher level [10]. This proposed relationship between coronary filling and coronary flow variations is similar to the elastance model proposed by Suga et al. [18] to describe ventricular function. During maximal vasodilatation intramural blood volume increases with coronary pressure, $P_d$, and therefore the elastance model predicts an increase in flow variations. This was indeed demonstrated by Krams et al. [11] in the isolated cat heart applying an external perfusion system with pressure control.

However, the interaction between myocardial contraction and intramural vessels is complicated and varies throughout systole [15]. In the beginning and end of systole left ventricular pressure is transmitted to coronary flow [9] and epicardial lymph pressure [5] while in mid-systole that effect is absent and the increased myocardial stiffness protects the intramural vessels against further compression. The interaction of these contraction-related effects has not yet been studied thoroughly.

Our data could not verify one of the observations on which the elastance model is based, namely that the pulsatility of flow in the hyperemic condition would increase with higher perfusion pressure. Using $PvI$ as a substitute for coronary flow amplitude we found that also in the absence of a stenosis flow pulsations were not related to mean coronary perfusion pressure $P_d$ during hyperemia (Figure 3.4). The range of perfusion pressures we covered was similar to that of Krams et al. [11], with stenotic vessels covering the lower range and revascularized and reference vessels the upper.

We demonstrated earlier that microvascular resistance at hyperemia depends on $P_d$ [20] and the earlier results of Krams et al. [11] may be explained by the pressure-dependence of microvascular resistance, rather than by an elastance-driven intramyocardial pump. Our data clearly demonstrate the effect of microvascular conductance on the pulsatile velocity index, which is in agreement with the intramyocardial pump model. However, our dataset provides no information about the compressive forces on the intramural blood vessels. Additional experiments in which these forces are modulated are required to further our understanding of that mechanism.

**Physiological interpretation of coronary pulsatile pressure index**

As has been observed previously [3], the distal coronary pressure waveform in the presence of a stenosis is substantially altered between rest and hyperemia. It changes from an aortic pressure pattern to that of left ventricular pressure and distal pressure starts to increase in systole before the aortic valve opens (see Figure 3.1). Prominent features in this transition are a steeper and greater drop from systolic to diastolic $P_d(t)$ and a slower decay of diastolic distal pressure. These features are augmented by stenosis severity and hyperemia in the presence of a stenosis (Figure 3.1). These changes in $P_d(t)$ are due to the fact that the stenosis represents a load for the intramyocardial pump and impedes the retrograde flow component [16, 17] which results in an increase of $PP_{Id}$ as shown in Figure 3.2A.
Since compression of intramural vessels is an important determinant of $PPI_d$, one would expect differences between the right and left coronary artery, since right ventricular pressure is much lower than left and therefore $\text{abs}(PPI_d-PPI_a)$ would be smaller for the right coronary artery than for the left. Such a difference was indeed found, as demonstrated in Figure 3.6A where $\text{abs}(PPI_d-PPI_a)$ is plotted as function of hyperemic SR. However, the right coronary artery in humans supplies not only the RV free wall but also a variable portion of the septum and LV free wall. Hence, the pressure and velocity pulsations in the right coronary artery are the result of a combination of different compression effects and it is not clear how these superimpose and affect each other. We have not sufficient data from the RCA to further explore these differences between the left and right coronary arterial system.

Recently changes in transmission of the high frequency content of aortic to distal pressure especially related to the dicrotic notch have been studied in relation to the functional significance of the stenosis as expressed by FFR [1]. A good correlation of $r = 0.81$ was found for this relationship. The damping of the dicrotic notch is yet another manifestation of the uncoupling of distal pressure from aortic pressure. However, the dicrotic notch only contributes to the pulsatile energy when its pressure variation is around the mean of the aortic or distal pressure. Moreover, even if this were the case, its contribution to the pulsatile energy would be small since the amplitude of pressure variation is small compared to the changes induced by the intramyocardial pump action.

**Relation between stenosis resistance at rest and during hyperemia**

We found an excellent incremental-linear relation between mean stenosis resistance at rest and hyperemia (Figure 3.5). Hyperemic SR was on average about 12% higher than SR at rest, which is to be expected since pressure drop increases more than proportionally with flow-velocity [8]. This linear relation between stenosis resistance at rest and hyperemia seems at odds with the nonlinear pressure drop-flow relation that characterizes a stenosis and is caused by separation losses due to the convergence and divergence of flow as described by the law of Bernoulli [4, 22]. However, for mild lesions the Bernoulli effect is small and stenosis resistance will only marginally increase with increasing flow. With higher stenosis severity the curvature of the stenosis pressure drop-velocity relationship will be steeper but the vasodilation-induced rise in flow velocity will be small, thereby limiting the Bernoulli effect on SR [12, 14]. Our present findings suggest that hyperemia is not a necessary condition to determine the severity of a stenosis based on its resistance. However, the practical utilization of this observation is limited by the fact that the pressure gradient is low at basal flow rates and small errors in pressure measurement would translate into relatively large errors in stenosis resistance.

**Relation between pulsatile resistance index and mean stenosis resistance**

Since the means of pressure and velocity define SR and PRI is derived from variations around the means of these signals, a correlation between PRI and SR is to be expected and our data show strong corresponding relationships. These correlations are different for the right and left coronary artery mainly due to the difference in $PPI_d$ for a given stenosis resistance, as discussed above. It is important to note that the correlations between hyperemic SR and PRI (LC: $r = 0.928$, RC: $r = 0.973$) are better than the respective correlations for the absolute value of the difference between $PPI_d$ and
PPIa (LC: r = 0.827, RC: r = 0.919) thanks to the incorporation of PVI data which has no linear relation with SR itself (LC: r = 0.287, RC: r = 0.331). This illustrates that a stenosis resistance influences the pulsatile energies of velocity and distal pressure in a related manner. Hence, the PRI better reflects the mechanisms underlying the stenosis effect on pulsatility of pressure and velocity waveforms than the signals themselves do separately.

**Usefulness of pulsatile indices for clinical decision-making**

There is a great need for decision support during the catheterization procedure with respect to ‘yes’ or ‘no’ treatment of a coronary lesion [8]. Methods that result in decision-support without the need for inducing hyperemia have a distinct advantage since there is no uncertainty about the dose of vasodilator to be administered [1]. The combined measurement of pressure and flow velocity provides a number of possibilities for indices that can assist clinical decision-making, including fractional flow reserve (pressure-based), FFR, coronary flow velocity reserve (velocity-based), CFVR, and hyperemic stenosis resistance (combined pressure and velocity). This study demonstrates the potential of a new index, PRI. The basic strength of this dynamic index is two-fold. In the first place, it is a quantity obtained at rest and correlates well with stenosis resistance at hyperemia. It has been demonstrated that especially for intermediate lesions hyperemic SR is a better predictor of reversible ischemia than FFR and CFVR [12]. By using PRI, no adenosine injections are needed to derive hyperemic SR. Secondly, the determination of the pulsatile indices is independent of drift in the pressure sensor, a recurrent problem when using sensor-equipped guidewires, which limits the usefulness of SR at baseline to predict SR at hyperemia.

With our increasing insight into the mechanisms determining the phasic patterns of coronary pressure and flow velocity in the diseased coronary artery, the future of clinical decision-making will most likely be assisted by a combination of indices derived from both mean and phasic characteristics of these signals.

**Conclusions**

In this study we demonstrate that pulsatile pressure and velocity indices are useful surrogates for changes in velocity and pressure amplitudes investigated in perfusion controlled studies. We find no dependency of PVI on distal pressure, but a good correlation between PVI and microvascular conductance, which disproves an accepted paradigm for explaining coronary flow pulsations. We further demonstrate that hyperemic stenosis resistance is well predicted by the pulsatile resistance index measured at baseline and therefore this index has high potential for clinical decision-making with respect to stenosis revascularization. More clinical studies are warranted to further substantiate these conclusions.
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