Minimal effect of collateral flow on coronary microvascular resistance in the presence of intermediate and noncritical coronary stenoses

Bart-Jan Verhoeff,1 Tim P. van de Hoef,1,2 Jos A. E. Spaan,2 Jan J. Piek,1 and Maria Siebes2

1Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; and
2Department of Biomedical Engineering and Physics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Verhoeff B, van de Hoef TP, Spaan JA, Piek JJ, Siebes M. Minimal effect of collateral flow on coronary microvascular resistance in the presence of intermediate and noncritical coronary stenoses. Am J Physiol Heart Circ Physiol 303: H422–H428, 2012. First published June 22, 2012; doi:10.1152/ajpheart.00003.2012.—Depending on stenosis severity, collateral flow can be a confounding factor in the determination of coronary hyperemic microvascular resistance (HMR). Under certain assumptions, the calculation of HMR can be corrected for collateral flow by incorporating the wedge pressure (Pw) in the calculation. However, although Pw > 25 mmHg is indicative of collateral flow, Pw does in part also reflect myocardial wall stress neglected in the assumptions. Therefore, the aim of this study was to establish whether adjusting HMR by Pw is pertinent for a diagnostically relevant range of stenosis severities as expressed by fractional flow reserve (FFR). Accordingly, intracoronary pressure and Doppler flow velocity were measured a total of 95 times in 29 patients distal to a coronary stenosis before and after stepwise percutaneous coronary intervention. HMR was calculated without (HMR) and with Pw-based adjustment for collateral flow (HMRc). FFR ranged from 0.3 to 1. HMR varied between 1 and 5 and HMRc between 0.5 and 4.2 mmHg·cm−1·s−1. HMR was about 37% higher than HMRc for stenoses with FFR < 0.6, but for FFR > 0.8, the relative difference was reduced to 4.4 ± 3.4%. In the diagnostically relevant range of FFR between 0.6 and 0.8, this difference was 16.5 ± 10.4%. In conclusion, Pw-based adjustment likely overestimates the effect of potential collateral flow and is not needed for the assessment of coronary HMR in the presence of a flow-limiting stenosis characterized by FFR between 0.6 and 0.8 or for nonsignificant lesions.

CORONARY MICROVASCULAR DYSFUNCTION is increasingly being recognized as a major contributor to myocardial ischemia (3) and is likely associated with an altered coronary hyperemic microvascular resistance (HMR). Hence, a reliable assessment of microvascular resistance is needed that accurately reflects the status of the microcirculation and supports further development of diagnostic tools for microvascular disease. Resistance of a vascular compartment is defined as the ratio of pressure drop over it and flow through it. Application of the resistance concept to the coronary circulation is challenging in the clinical setting, since volume flow cannot practically be measured directly and coronary back pressure is governed by multiple factors including microvascular conductance and extravascular compressive forces (16, 17, 32, 37). At present, two guidewire-based systems are capable of the combined measurement of pressure and a surrogate of flow through a coronary stenosis. In the first system, flow velocity is measured by a Doppler crystal next to a pressure sensor (31, 35). The second system exploits the temperature sensitivity of the pressure sensor to determine the mean transit time of a temperature change induced by a bolus of saline (10). The corresponding indexes of HMR are respectively defined as the mean distal pressure (Pd) divided by mean distal flow velocity (35) or divided by the inverse of mean transit time [index of microvascular resistance (IMR)] (10) during maximal vasodilation. The entrance of the microcirculation is not uniquely defined. Collateral flow presumably enters the myocardium via vessels downstream of the measurement location, and epicardial flow measurement may then underestimate total microvascular perfusion, resulting in an overestimation of microvascular resistance. Coronary wedge pressure (Pw) measured during balloon occlusion of the epicardial vessel is assumed to represent an index of collateral flow that can be used to adjust coronary microvascular resistance values obtained from epicardial measurements (1, 9). Importantly, the derivation of a Pw-based adjustment for potential collateral flow is based on the assumption that the resistance of the diluted coronary microvascular bed is fixed. This assumption contradicts abundant reports in the physiological literature indicating that resistance vessels without tone are distensible and their diameter is pressure dependent (17, 32). In addition, extravascular compressive forces in the myocardium also contribute to the value of Pw even in the absence of collateral flow (8), and therefore, Pw overestimates the collateral flow effect (32).

Hence, the assessment of coronary microvascular resistance is hampered by the uncertainty associated with the potential error induced by the presence of collateral flow downstream of a stenosis, and conflicting definitions have been used in recent reports of clinical investigations (1, 10, 18, 35). Obviously, the importance of the effect of collateral flow increases with decreasing distal coronary pressures, but it is important to establish in what range of stenosis severities this effect should be considered significant in daily clinical practice.

The main objective of this study was to analyze whether incorporation of potential collateral flow in the definition of hyperemic coronary microvascular resistance is necessary in the presence of stenoses in the diagnostically relevant range, as expressed by fractional flow reserve (FFR). For that purpose, we established the relationship between FFR and HMR calculated both with and without Pw-based adjustment and assessed the relative difference between the two quantities, which represents an estimate of the error induced by neglecting the effect of collateral flow.
COLLATERAL FLOW AND CORONARY MICROVASCULAR RESISTANCE

Study population. Twenty-nine patients with stable angina (Canadian Cardiovascular Society classes 1 through 3) and a single de novo lesion in a native coronary vessel, who were scheduled for elective percutaneous coronary intervention (PCI), participated in this study. Patients with left main coronary artery stenosis, serial or subtotal lesions in the target vessel, diffuse disease, left ventricular ejection fraction <30%, severe valve abnormalities, hypertrophic cardiomyopathy, abnormal clotting profiles, recent myocardial infarction (<6 wk), or severe renal dysfunction were excluded. Antiplatelet and antiplatelet medications were continued. The Institutional Ethical Review Board approved the study, and all patients gave written informed consent.

Hemodynamic measurements. Aortic pressure (P_a) was measured via a guiding catheter placed in the coronary ostium by standard femoral approach. P_d and flow velocity (v) were measured using a 0.014-in. guidewire equipped with both a Doppler velocity probe and a pressure sensor (Combowire, Volcano, San Diego, CA). The wire was positioned in the target vessel with both sensors at least three to five vessel diameters distal to the coronary stenosis. All hemodynamic signals were processed with their respective instrument consoles and recorded on a personal computer together with the electrocardiogram after 12-bit analog-to-digital conversion at 120 Hz.

Study protocol. An intracoronary bolus of nitroglycerin (0.1 mg) was administered at the start of the procedure and repeated after 30 min. Hemodynamic signals were continuously recorded throughout the hyperemic response induced by an intracoronary bolus of 20 to 40 μg adenosine (5). Sequential measurements were obtained before and after revascularization by balloon angioplasty followed by stent placement. Coronary P_w and P_a were recorded after at least a 30-s balloon inflation.

Hemodynamic parameters and resistance models. The relevant hemodynamic models used in the literature in relation to measuring coronary HMR are illustrated in Fig. 1. The corresponding equations are presented in the APPENDIX.

Figure 1A illustrates the case in which collateral flow is neglected and all blood that passes through the microcirculation also passes through the stenosis in the feeding artery. Hyperemic stenosis resistance (HSR) and microvascular resistance (HMR) follow simply from the ratio between pressure drop across and flow velocity through these compartments. Central venous pressure (P_v) was not measured and as a first approximation was assumed to be zero. Figure 1B reflects the situation in which collateral vessels, indicated by collateral resistance (R_c), are present. These collateral vessels connect the perfusion area distal to the stenosis, represented by HMR_c, with the contralateral region, HMR_x. In this situation, the calculation of HMR_c is adjusted by P_w (Eq. A5). The collateral flow index (CFI) expresses the ratio between the collateral flow and total flow through HMR_c based on pressure measurements including P_w (Eq. A3) (29).

The relative difference between HMR and HMR_c was determined as a function of the severity of the epicardial stenosis represented by FFR = P_d/P_a during hyperemia.

Data analysis. To analyze the relation between HMR and HMR_c, respectively, and FFR for comparable values of functional stenosis severities, the data were stratified by HSR. The bin size varied between 0.1 and 1 mmHg·cm⁻¹·s as defined in Fig. 3 legend, such that the number of data points within each bin remained sufficiently high to allow curve fitting. Within each bin, the data were fitted with the hyperbolic function FFR = R/(R + a), corresponding to Eq. A7. Here, R represents either HMR or HMR_c according to Eqs. A4 and A5; respectively, and the coefficient a represents the fitted value for HSR within the respective bin.

Data were also dichotomized based on values of P_w larger or smaller than 25 mmHg. This value has been described in the literature as a threshold to indicate the presence of collateral flow (26, 29, 36), but it also includes the rightward shift in the hyperemic coronary pressure-flow relation induced by contraction-related wall stress (8, 32).

Statistical methods. All data are presented as means ± SD. Means were compared by two-sided paired or unpaired t-test (SPSS v. 12) as appropriate, and curve fitting was performed using scientific plotting software (Grapher v. 7, Golden Software, Boulder, CO). A value of P < 0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics are listed in Table 1. A total of 95 measurements were obtained in 29 coronary arteries. One patient was treated in two separate sessions. There were no differences between groups when the patient cohort was stratified by P_w ≤ 25 mmHg and P_w > 25 mmHg. The study lesions were localized in the left anterior descending (n = 14), left circumflex (n = 7), intermediate branch (n = 1), and right coronary artery (n = 7).

P_w obtained before treatment is plotted versus FFR in Fig. 2, with white circles for P_w ≤ 25 mmHg and black circles for higher values. Mean P_w was 18.1 ± 4.7 mmHg (n = 12) for

Table 1. Clinical characteristics

| Subjects (n) | 29 |
| Age, yr | 59 (SD 8) |
| Men | 20 (69%) |
| Coronary risk factors |  |
| Cigarette smoking | 11 (38%) |
| Hypertension | 8 (28%) |
| Positive family history | 14 (48%) |
| Hyperlipidemia | 19 (66%) |
| Diabetes mellitus | 6 (21%) |
| Prior myocardial infarction >6 wk | 9 (31%) |
| Prior coronary angioplasty in other vessel | 6 (21%) |
| Medication |  |
| β-Blockers | 27 (93%) |
| Nitrates | 17 (59%) |
| Calcium antagonists | 12 (41%) |
| Angiotensin-converting enzyme inhibitors | 4 (14%) |
| Lipid lowering drugs | 25 (86%) |
| Aspirin | 28 (97%) |

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Fig. 1. Electrical analogs of coronary resistance models. A: model of the coronary circulation consisting of 2 resistances in series. Hyperemic stenosis resistance (HSR) and hyperemic microvascular resistance (HMR) are calculated analogous to Ohm’s law. P_a, aortic pressure; P_d, distal pressure; P_v, venous pressure; v, flow velocity. B: coronary resistance model including collateral flow from a parallel branch. This model was used to derive HMR_c with an adjustment for collateral flow. HMR_x, minimal microvascular resistance of adjacent perfusion territory (unknown); R_c, collateral resistance.
P_{w} < 25 \text{ mmHg} and 33.0 \pm 6.0 \text{ mmHg} (n = 17) for P_{w} > 25 \text{ mmHg}. Neither in the entire data set nor in the subgroups defined by P_{w} above or below 25 mmHg was P_{w} related to FFR (P = 0.2 and 0.7, respectively).

HMR before treatment was 2.9 \pm 1.4 \text{ mmHg} \cdot \text{cm}^{-1} \cdot \text{s} (range, 1.02 to 5.8 \text{ mmHg} \cdot \text{cm}^{-1} \cdot \text{s}) and was not different between groups separated by P_{w} = 25 \text{ mmHg} (P = 0.09). Corresponding FFR was 0.58 \pm 0.17, and HSR was 2.74 \pm 2.47 \text{ mmHg} \cdot \text{cm}^{-1} \cdot \text{s}. There was no significant difference due to the presence of risk factors such as diabetes mellitus or hypertension (P = 0.3 and P = 0.8, respectively).

The relationship between hyperemic coronary microvascular resistance and FFR is illustrated in Fig. 3, showing FFR as a function of HMR (Fig. 3A) and HMRC (Fig. 3B) for all data before and after stepwise PCI. For a given stenosis severity, characterized by a narrow range of HSR, FFR increased with HMR as expected, regardless of its definition. The fitted curves yielded correlation coefficients between 0.94 and 0.99. Note that especially for FFR < 0.6, HMRC was lower than HMR for the same FFR, resulting in steeper relationships between microvascular resistance and FFR (Fig. 3B). The dashed curves represent the theoretical relationship for HSR = 0.8 \text{ mmHg} \cdot \text{cm}^{-1} \cdot \text{s}, the threshold value for inducible ischemia as previously reported (21).

The relative difference between the two methods of calculating HMR (i.e., Eqs. 4A and 5) is illustrated in Fig. 4 for all measurements. The theoretical relation for CFI = 0.1 (solid curve) forms a lower bound for all data, whereas the relation for CFI = 0.21 (dashed curve) represents a fair boundary between the data points stratified by P_{w} = 25 \text{ mmHg}. Clearly, the relative difference between HMR and HMRC becomes larger with increasing stenosis severity as expressed by FFR, both theoretically and experimentally.

Overall, the relative difference between HMR and HMRC was 33% before treatment, 10% after balloon angioplasty, and less than 5% after stent placement. For severe lesions with FFR \leq 0.6, the overall relative difference was 37 \pm 23% and was larger (P < 0.01) for P_{w} > 25 \text{ mmHg} (49 \pm 22%) than for P_{w} < 25 \text{ mmHg} (22 \pm 14%). For intermediate lesions as indicated by FFR between 0.6 and 0.8, the mean difference between HMR and HMRC amounted to 16.5 \pm 10.4% and was 9.0 \pm 3.0% for P_{w} < 25 \text{ mmHg} vs. 20.8 \pm 10.7% for P_{w} > 25 \text{ mmHg} (P < 0.01). In fact, for FFR > 0.8, the overall mean difference decreased to 4.4 \pm 3.4%, indicating that the definition of microvascular resistance is hardly relevant in the absence of a flow-limiting stenosis.

**DISCUSSION**

The major finding of this study is that incorporating P_{w} as an estimated contribution of collateral blood flow does not substantially influence the assessment of coronary HMR when FFR > 0.6. The values for HMR and HMRC in the range of FFR from 0.6 to 0.8 differed not more than 16.5% and for FFR > 0.8 not more than 4.4% between the two methods. Hence, either HMR or HMRC can be used to quantify coronary HMR in the presence of a stenosis in the diagnostically relevant range or after PCI. Considering that a potential collateral contribution is likely overestimated by incorporating P_{w}, especially in patients with elevated wall stress such as in left ventricular hypertrophy (8, 32), we recommend against P_{w}-based adjust-
increase resistance especially at the subendocardium, and a rise in distending pressure inflates the passive microvessels, thereby reducing resistance (13, 17, 32, 37). These sensitivities of microvascular resistance to external stress and intraluminal pressure are mutually dependent as demonstrated by microsphere studies in animals (11). These mechanical determinants of coronary resistance yield a pressure-flow relation that is straight in the physiological range of arterial pressures, but is curvilinear for pressures below 40 mmHg. This has been clearly demonstrated by observations on pressure-flow relations obtained under experimental conditions where collateral effects were absent because of lack of a pressure gradient between the epicardial arteries (7, 13, 19). Moreover, the coronary pressure-flow relation is also shifted rightward in ventricles with elevated wall stress, e.g., because of hypertrophy, again without any contribution of collateral flow (12). Hence, a straight pressure-flow relationship in the physiological range of perfusion pressures is no proof of a constant coronary resistance, nor does the existence of a nonzero $P_w$ exclusively represent the effect of collateral flow.

Interpretational disparity regarding the determinants of $P_w$ has unfortunately resulted in different definitions for an index of hyperemic coronary microvascular resistance in the recent literature (1, 9, 10, 18, 31, 32, 35), and clinical data have been inconsistently reported with and without a $P_w$-based correction for collateral flow (2–6, 8, 22). Obviously, $P_w$ will be elevated in the presence of functional collaterals, but we argue that below a threshold value of 25 mmHg, $P_w$ may well be fully determined by factors related to the mechanics of cardiac contraction (8, 32).

This reasoning is in line with several clinical studies where it was concluded that collateral flow is essentially absent when $P_w$ is lower than 25 mmHg (22, 25, 30, 34, 38). Moreover, this value agrees well with the intercept pressure measured in experimental studies on the effects of wall stress and intravascular pressure (7). Therefore, the data in the present study were divided into one group, where $P_w$ was lower than 25 mmHg, and one with higher values, assuming that relevant collateral function would only be present in the high $P_w$ group. Yet even for these higher $P_w$ values, the relative error for intermediate stenoses remains within acceptable levels compared with the wide variation in HMR found in patients (20).

Study limitations. Several limitations require consideration. We did not subtract actual central $P_c$ from the measured proximal and $P_d$ to derive FFR (24) since it was not measured. Subtracting a fixed $P_c$ of 5 mmHg in Eqs. A1 and A3 slightly shifted individual data to lower values, and the relative difference between HMR and HMRc dropped from 16.5 to 13% for FFR between 0.6 and 0.8. However, as expected, this did not alter the overall relationship between FFR and HMR or HMRc.

The present study was performed in a select group of clinically stable patients with single- or two- vessel coronary artery disease and without hypertrophic cardiomyopathy or other obvious comorbidity associated with microvascular dysfunction that would be reflected by elevated values of HMR (3). Despite the absence of such pathological conditions, our results demonstrated a significant dependence of FFR on hyperemic coronary microvascular resistance. Our findings may therefore be even more pertinent in an extended clinical setting with higher prevalence of microvascular impairment (3). In fact, even in a population of healthy volunteers a natural
variation in hyperemic coronary resistance exists, as measured by positron emission tomography (4). Furthermore, age has been identified as a factor that may affect microvascular resistance (4, 14). An elevated HMR, as assessed with a dual-sensor guidewire immediately after PCI, has been associated with microvascular dysfunction in patients with ST-segment elevation myocardial infarction, and predictive values have been established for extent of transmural infarction and recovery of left ventricular function (2, 15, 39). HMR may thus be a useful parameter for early risk stratification in patients with acute myocardial infarction. However, more studies are needed to identify abnormal values for HMR.

The appropriate dose for intracoronary injection of adenosine has been studied extensively (5) and it was shown that the intracoronary dose we applied achieved full dilatation comparable to intravenous administration for the stenosis range studied here. Moreover, HMR calculated either way would be affected similarly in case maximal hyperemia was not achieved, thereby minimizing its influence on the relative difference between microvascular resistances.

Collateral flow has not been measured directly in this study, a limitation that is shared by several key publications on the matter (1, 9, 27). In a recent study employing a mock circulation, collateral flow could be measured directly (23). At FFR = 0.74, the maximal collateral contribution to total microvascular flow did not exceed 8%. This corroborates our findings that the difference between HMR and HMRc is small in the presence of such an intermediate stenosis.

In this study, most of the data for FFR >0.7 come from coronary vessels that were treated by PCI. On theoretical grounds it is, however, not to be expected that our results would be different when vessels are included with FFR > 0.7 without treatment, since HMR and HMRc converge to the same expression with increasing FFR, which is demonstrated by the theoretical curves in Fig. 4.

Finally, we only evaluated the effect of Pw-based adjustment for collateral flow on the velocity-derived HMR. Conceptually, a similar effect of collateral flow incorporation can be expected for the thermodilution-derived IMR, since the main difference is that flow is approximated by the inverse of mean transit time instead of by flow velocity. Hence, the outcome of the study would not be different when thermodilution had been applied.

Clinical implications. Coronary microvascular dysfunction has important emerging implications in clinical diagnosis, risk stratification, and prognosis of cardiac patients (3, 15, 28, 39). Assessment of small vessel disease requires quantification of coronary microvascular resistance, especially in the absence of epicardial disease or with a moderate stenosis resistance. As we have demonstrated, the manner of calculating HMR is less and less relevant with a lower pressure drop over the stenosis, i.e., FFR closer to 1. When we consider that microvascular resistance varied by 400% within our study group, the percent uncertainty in microvascular resistance resulting from neglecting possible collateral flow seems rather acceptable for diagnostically relevant lesions with FFR > 0.6. Moreover, a recent study reported a large overlap in thermodilution-based IMR between patients with and without epicardial atherosclerosis (18). Clinical decision making could be fine tuned by a HMR determination in the sense that in the presence of higher microvascular resistance, which leads to a higher value of FFR, PCI would be advised at a higher level than with lower HMR (23). This agrees with our earlier conclusion that HMR plays a role in the disparity between FFR and coronary flow velocity reserve (20). Microvascular resistance, calculated according to HMR, is higher in more flow-limiting stenoses, which may have pathophysiological implications. This effect dissipated with calculation according to HMRc, thus after correction for Pw. This is probably due to the fact that the underlying principles of HMRc ignore the effects of cardiac contraction on hyperemic myocardial perfusion, although these effects have been well documented. The present finding that HMR and HMRc are practically equal for higher values of FFR underlines the conclusion that HMR in the treated vessel after PCI is lower than in the reference vessel of the same heart (35).

It is important to realize that in case collateral flow does contribute to microvascular flow in the target region, both models are flawed and true microvascular resistance cannot be determined without additional direct measurement of collateral or microvascular flow. Not adjusting for potential collateral flow by subtracting Pw will preserve physiological behavior in terms of the pressure dependence of hyperemic coronary resistance and prevent overcorrection in case of enhanced wall stress. This concept applies to both velocity (HMR) and thermodilution (IMR)-based indexes.

Conclusions. This study demonstrates that the diagnosis of increased coronary HMR is independent of an adjustment for potential collateral flow, not only for nonsignificant lesions (FFR >0.8) but also in the presence of diagnostically relevant lesions (FFR between 0.6 and 0.8).

APPENDIX

All calculations assume maximal vasodilation of the coronary circulation. Hyperemia was defined as the period of the highest average flow velocity during three consecutive heart beats after adenosine administration. FFR and HSR were calculated as previously defined (21, 27):

\[
\text{FFR} = \frac{P_d - P_v}{P_a - P_v} \quad (A1)
\]

\[
\text{HSR} = \frac{P_a - P_d}{v} \quad (A2)
\]

CFI was calculated from pressure measurements at the end of the balloon occlusion as

\[
\text{CFI} = \frac{P_a - P_v}{P_a - P_v} \quad (A3)
\]

Central Pw was as first approximation assumed to be negligible. Coronary HMR was calculated according to two conceptual models of the coronary circulation as depicted in Fig. 1. First, a resistance model including the proximal stenosis resistance, HSR, in series with a lumped microvascular resistance was used (Fig. 1A), yielding HMR as the ratio of Pa and flow velocity (21, 31, 35):

\[
\text{HMR} = \frac{P_a}{v} \quad (A4)
\]

Next, microvascular resistance was calculated according to a model incorporating Rc (Fig. 1B). Assuming that minimal coronary microvascular resistance is constant regardless of the prevailing perfusion pressure in the distal microvascular bed (1, 9, 27), the following expression for the hyperemic resistance of the collateral-receiving microvascular bed can be derived:
**REFERENCES**


