

Comprehensive physiological evaluation of epicardial and microvascular coronary domains using vascular conductance and zero flow pressure



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This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/148th_issue/272

KEYWORDS

- fractional flow reserve
- other technique
- QCA
- stable angina

Abstract

Aims: Assessment of the coronary circulation has been based largely on pressure ratios (epicardial) and resistance (micro-vessels). Simultaneous assessment of epicardial (C_{EPI}) and microvascular conductance (C_{MICRO}) provides an intuitive approach using the same units for both coronary domains and expressing the actual deliverability of blood. The aim of this study was to develop a novel integral method for assessing the functional severity of epicardial and microvascular disease.

Methods and results: We performed intracoronary pressure and Doppler flow velocity measurements in 403 vessels in 261 patients with stable coronary artery disease. Hyperaemic mid-to-late diastolic pressure and flow velocity (PV) relationships were calculated. The slope of the aortic PV indicates the overall conductance and the slope of the distal PV relationship represents C_{MICRO} . The intercept with the x-axis represents zero-flow pressure (Pzf). C_{EPI} was derived from microvascular and overall conductance. Median C_{EPI} was higher compared to C_{MICRO} (4.2 [2.1-8.0] versus 1.3 [1.0-1.7] cm/s/mmHg, $p < 0.001$). C_{MICRO} was independent of stenosis severity (1.3 [1.0-1.7] in $FFR \leq 0.80$ versus 1.4 [1.0-1.8] in $FFR > 0.8$, $p = 0.797$). ROC curves (using FFR and HSR concordant vessels as standard) demonstrated an excellent ability of C_{EPI} to characterise significant stenoses (AUC 0.93). When $C_{EPI} < C_{MICRO}$, a decrease in flow velocity and coronary pressure (optimal cut-off value 0.97, AUC 0.90) was demonstrated.

Conclusions: A comprehensive assessment of separate C_{EPI} and C_{MICRO} was feasible. C_{EPI} has a remarkable diagnostic efficiency to detect a clinically relevant stenosis. When $C_{EPI} < C_{MICRO}$, distal flow and pressure decrease steeply, indicating myocardial ischaemia. C_{MICRO} can be used to explore the severity of microvascular disease.

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Abbreviations

AUC	area under the curve
C_{EPI}	epicardial conductance
CFVR	coronary flow velocity reserve
C_{MICRO}	microvascular conductance
C_{OVERALL}	overall conductance
FFR	fractional flow reserve
HMR	hyperaemic microvascular resistance
HSR	hyperaemic stenosis resistance
IHD	ischaemic heart disease
IHDVPS	instantaneous hyperaemic diastolic flow velocity-pressure slope
PCI	percutaneous coronary intervention
Pzf	zero-flow pressure
QCA	quantitative coronary angiography
ROC	receiver operating characteristic
%DS	percent diameter stenosis

Introduction

The current role of coronary physiology is to perform functional assessment of epicardial vessel disease to guide coronary revascularisation¹. However, it is foreseeable that, in the near future, interrogation of the coronary microcirculation will also be routinely performed, as microvascular dysfunction is an acknowledged cause of cardiac events in ischaemic heart disease (IHD)². Methods to assess both epicardial stenosis severity and microvascular disease are lacking. Fractional flow reserve (FFR) provides valuable information on the haemodynamic relevance of stenotic epicardial vessels but does not interrogate the microcirculation; coronary flow velocity reserve (CFVR) may be used to interrogate the microcirculation in the absence of epicardial stenoses³. At present, assessment of the microcirculation is based on the calculation of vascular resistance⁴⁻⁷. An alternative approach is the use of vascular diastolic conductance (the inverse of coronary resistance). Conductance assesses the coronary function in terms of its primary purpose, namely delivery of myocardial blood flow. A higher conductance expresses a greater myocardial blood supply. Theoretically, conductance can be calculated to estimate both epicardial and microcirculatory domains. Calculation of microcirculatory conductance (C_{MICRO}) is feasible and reflects the degree of structural remodelling of arterioles and capillaries⁸. However, until now, a method to calculate separate epicardial conductance (C_{EPI}) has been unavailable.

The main aim of this study was to develop a method for the separate assessment of C_{EPI} and C_{MICRO} to allow a comprehensive assessment of the coronary circulation in patients with IHD.

Methods

DATA SOURCE

We acquired pressure and Doppler flow velocity measurements from 308 patients with stable angina pectoris included in an ongoing large international registry (the Iberian-Dutch-English [IDEAL] registry) (**Figure 1**). Prospective patient data were

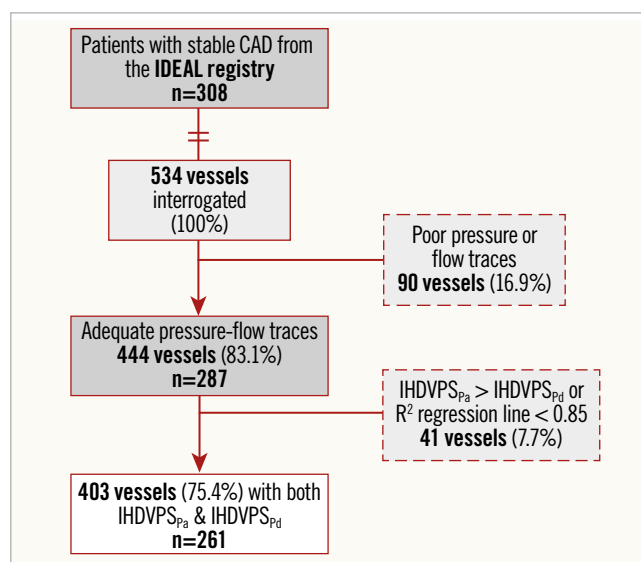


Figure 1. Study flow chart. CAD: coronary artery disease; IDEAL study: Iberian-Dutch-English study⁹; IHDVPS_{pa}: Instantaneous Hyperaemic Diastolic Velocity Pressure Slope index calculated using aortic pressure; IHDVPS_{pd}: Instantaneous Hyperaemic Diastolic Velocity Pressure Slope index calculated using distal pressure

obtained in four different centres - the VU University Medical Center, Amsterdam, the Netherlands (n=120), the Academic Medical Centre, Amsterdam, the Netherlands (n=92), Imperial College London, London, United Kingdom (n=72), and Hospital Clínico San Carlos, Madrid, Spain (n=24). A detailed description of the IDEAL registry was published previously⁹.

CARDIAC CATHETERISATION AND HAEMODYNAMIC MEASUREMENTS

Pressure and Doppler flow velocity measurements were performed with the ComboWire[®] XT (Philips/Volcano, San Diego, CA, USA) in a standardised fashion⁹. Based on the fact that in the coronary vessels flow velocity is kept relatively constant due to proportionality between subtended myocardial mass and coronary luminal diameter, distal flow velocity was used as a surrogate for proximal flow velocity^{10,11}. Hyperaemia was induced by the administration of adenosine (two-minute infusion with 140 µg/kg/min i.v. or a bolus 60-150 µg i.c.). Finally, the amount of potential drift was assessed. All measurements were directly extracted from the device console (ComboMap[®]; Philips/Volcano). Data were analysed with specialised software (MATLAB; MathWorks, Inc., Natick, MA, USA). Quantitative coronary angiography (QCA) was performed off-line to assess percent diameter stenosis (%DS) using an automated contour analysis system (CAAS II; Pie Medical, Maastricht, the Netherlands).

CALCULATION OF INTRACORONARY PHYSIOLOGY INDICES

Calculation of coronary physiology indices was performed off-line from digitised pressure and flow recordings^{12,13}. Whenever

the difference between aortic pressure (Pa) and distal pressure (Pd) at the level of the guiding catheter was >2 mmHg, it was assumed that this was the result of Pd drift, and all physiological indices using pressure were recalculated after correcting Pd¹⁴. FFR was calculated as the Pd/Pa ratio during maximal hyperaemia. We used the lowest stable value of FFR. Whole cycle hyperaemic stenosis resistance (HSR) was calculated as mean trans-stenotic pressure gradient (Pa-Pd) divided by mean flow velocity. Coronary flow velocity reserve (CFVR) was calculated as the ratio of mean hyperaemic and baseline flow velocity. Whole cycle hyperaemic microvascular resistance (HMR) was calculated as mean Pd divided by mean flow velocity.

CALCULATION OF INDICES OF CONDUCTANCE

Vascular conductance (**Figure 2**) was derived by means of instantaneous hyperaemic diastolic flow velocity-pressure slope (IHDVPS) using a dedicated automated analysis programme written using the R statistical programme (statistical software R version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria, 2013). IHDVPS is defined as the slope (β -coefficient) of the relationship between hyperaemic intracoronary pressure and flow in mid to end diastole, which is displayed by a single regression line ($y=a + \beta x$) expressed in cm/s/mmHg (**Figure 3**)¹⁵. The diastolic period was recognised using the peak flow velocity. The R² regression coefficient was used to evaluate the linearity of the relationship between diastolic hyperaemic pressure and flow (cut-off value of R² of ≥ 0.85). Hyperaemic Pa was determined to calculate the overall conductance ($C_{OVERALL}$)^{15,16} and hyperaemic Pd to calculate C_{MICRO} . Using an electric circuit analogy, the coronary circulation can be described as a resistive (R) model (**Figure 2**) in which:

$$R_{OVERALL} = R_{EPI} + R_{MICRO}$$

Since conductance (C) is the inverse of resistance,

$$\frac{1}{R_{OVERALL}} = \frac{1}{R_{EPI} + R_{MICRO}} \Rightarrow \frac{1}{R_{EPI} + R_{MICRO}} = C_{OVERALL} = \frac{1}{\frac{1}{C_{EPI}} + \frac{1}{C_{MICRO}}}$$

where C represents $C_{OVERALL}$, C_{EPI} and C_{MICRO} (**Figure 2**).

Further elaboration of this equation allows calculation of separate epicardial conductance:

$$C_{OVERALL} = \frac{1}{\frac{1}{C_{EPI}} + \frac{1}{C_{MICRO}}} \Rightarrow C_{OVERALL} = \frac{C_{EPI} C_{MICRO}}{C_{EPI} + C_{MICRO}}$$

From this C_{EPI} can be readily calculated:

$$C_{EPI} = \frac{C_{MICRO} C_{OVERALL}}{C_{OVERALL} - C_{MICRO}}$$

which is transformed for clarity purposes, multiplying numerator and denominator by -1 , in order to obtain the final, equivalent, expression:

$$C_{EPI} = \frac{C_{MICRO} C_{OVERALL}}{C_{MICRO} - C_{OVERALL}}$$

Actual values of epicardial conductance are obtained from IHDVPS as follows:

$$C_{EPI} = \frac{IHDVPS_{Pd} IHDVPS_{Pa}}{IHDVPS_{Pd} - IHDVPS_{Pa}}$$

To validate C_{EPI} , two clinically validated indices of stenosis severity were used, to obtain the optimal reference standard - FFR and HSR. Only vessels with a concordant value of both indices

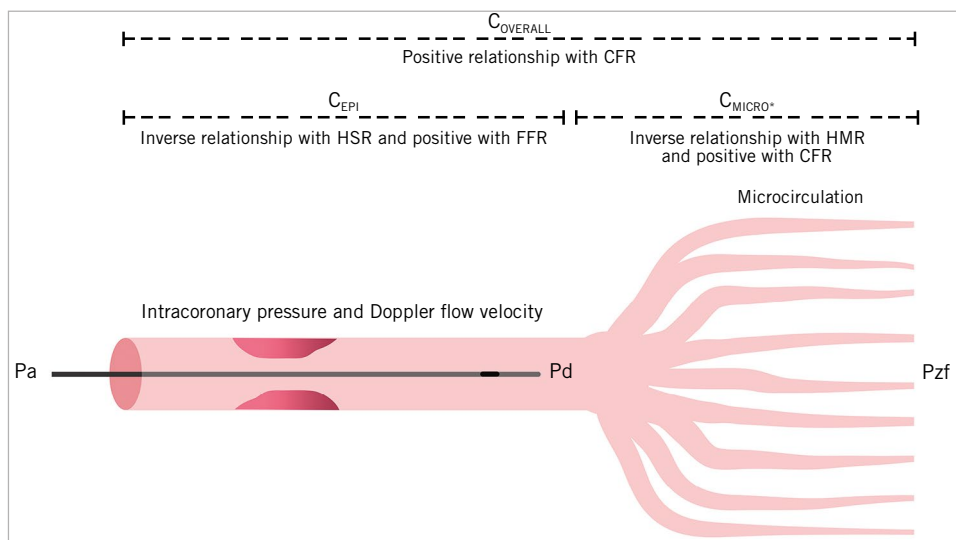


Figure 2. Overview of the indices of coronary conductance. Schematic depiction of the coronary circulation illustrating the different domains explored with vascular conductance and other haemodynamic indices mentioned in this study. C_{EPI} : epicardial conductance; CFR: coronary flow reserve; C_{MICRO} : microvascular conductance; $C_{OVERALL}$: overall conductance; FFR: fractional flow reserve; HMR: hyperaemic microvascular resistance; HSR: hyperaemic stenosis resistance; Pa: aortic pressure; Pd: distal pressure; Pzf: zero-flow pressure;

* C_{MICRO} independent of stenosis severity

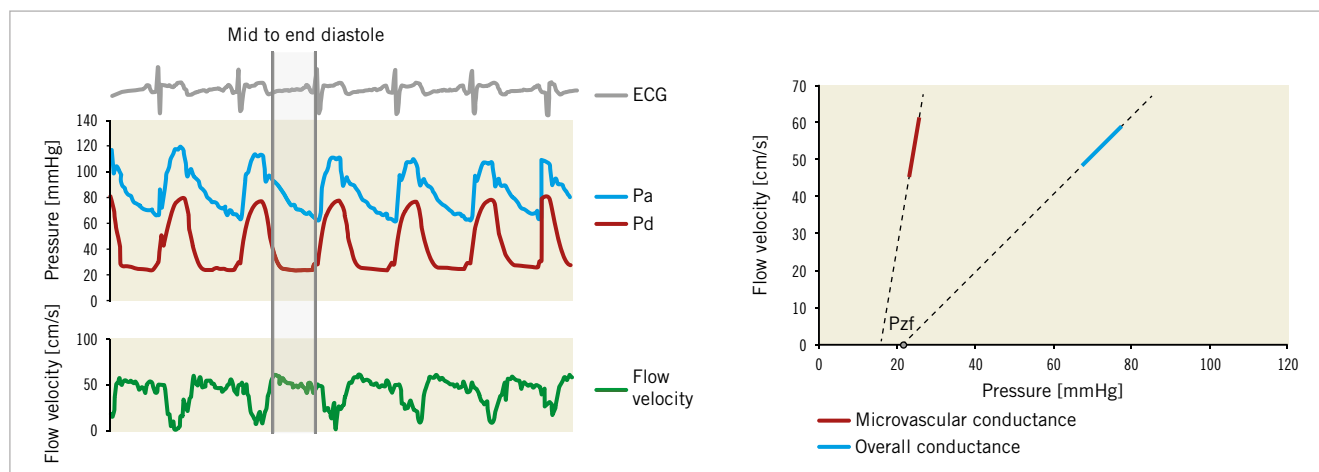


Figure 3. Acquisition and calculation of coronary conductance. The marked area is the mid to end-diastolic part for calculation of conductance. Doppler flow velocity and pressure are plotted during one cardiac beat and the linear relationship between pressure and flow in this period is displayed. The β -coefficient of this line represents overall (blue) and microvascular conductance (red) expressed in cm/s/mmHg. Pzf: zero-flow pressure

were used to create a valid cut-off value for C_{EPI} . Zero-flow pressure (Pzf) was extrapolated from the regression line of the relationship between pressure and flow and is defined as the intercept of the regression line with the pressure axis.

STATISTICAL ANALYSIS

SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis of our data. Continuous variables were described as mean \pm SD or median (interquartile range [IQR]), depending on their normality, and categorical variables as frequency (percentage). Spearman's correlation was used to examine the correlation between the different haemodynamic parameters. Associations between parameters measured on vessel level were assessed using generalised estimating equations with an exchangeable correlation matrix to account for correlation of the dependent variable determined for multiple vessels within the same patient. Differences in conductance between pairs of groups were assessed by an independent samples t-test or Mann-Whitney U test as appropriate. In case of multiple groups, ANOVA with *post hoc* Bonferroni or Kruskal-Wallis test was used accordingly. Receiver operating characteristic (ROC) curves with the method of DeLong for the calculation of the standard error of the area under the curve (AUC) and of the difference between two AUCs were used to compare the diagnostic efficiency of the indices. To calculate the optimal cut-off value, Youden's index was used. A value of $p < 0.05$ was considered statistically significant.

Results

PATIENT AND VESSEL CHARACTERISTICS

Figure 1 summarises the study population selection workflow. All values with $IHDVPS_{Pa} > IHDVPS_{Pd}$ were excluded. The remaining 403 (75.4%) vessels in 261 patients constituted the study population.

The patient population consisted mostly of men (64.6%) with an average age of 60.2 ± 9.3 (**Table 1**). The left anterior descending artery (LAD) was the most frequently investigated vessel ($n=171$, 42.4%). Median FFR was 0.93 (0.84-0.97) in the overall population and was higher than reported in other series as a result of the inclusion of 202 vessels without severe angiographic lesions. The majority of vessels ($n=335$, 83.1%) had an FFR > 0.80 , while 66 (16.4%) had an FFR ≤ 0.8 . Median FFR in the FFR ≤ 0.8 group was 0.67 (0.54-0.75). There were 52 (13.0%) vessels with FFR ≤ 0.75 and 39 (9.7%) with FFR ≤ 0.70 . In two vessels FFR measurements were not possible. There were 202 (50.1%) vessels without angiographically focal intermediate stenoses (50-90%). %DS was assessed in 195 (48.4%) vessels with angiographically intermediate stenoses with a mean of 53.5 ± 15.9 .

Table 1. Baseline characteristics.

Patients (n=261)		Mean, median or count
Age, years		60.7 \pm 10.0
Gender, male		172 (66.4%)
Hypertension		134 (51.7%)
Hyperlipidaemia		136 (52.5%)
BMI		26.8 [24.49-29.28]
Current smoker		109 (42.1%)
DM 2		57 (22.0%)
Chronic renal failure		4 (1.5%)
Family history	CAD	115 (44.4%)
	LVEF $< 30\%$	2 (0.8%)
	Stable angina	248 (95.8%)
	Unstable angina	10 (3.9%)
BMI: body mass index; CAD: coronary artery disease; DM 2: diabetes mellitus type 2; LVEF: left ventricle ejection fraction		

MICROVASCULAR CONDUCTANCE

C_{MICRO} in the overall population was 1.3 (1.0-1.7) cm/s/mmHg. C_{MICRO} values were not influenced by the presence of epicardial disease (1.3 [1.0-1.7] in angiographically stenotic versus 1.3 [1.0-1.7] in non-stenotic vessels, $p=0.932$), nor influenced by stenosis severity (as judged by $\%DS \geq$ or <50 , respectively 1.3 [1.0-1.7] versus 1.3 [1.0-1.7], $p=0.682$). Similar values of mean C_{MICRO} were observed in vessels with an FFR \leq or >0.80 (respectively 1.3 [1.0-1.7] versus 1.4 [1.0-1.8], $p=0.797$) or \leq or >0.70 (respectively 1.3 [1.0-1.7] versus 1.4 [1.0-1.8], $p=0.697$). In patients with abnormal CFVR (<2.0), C_{OVERALL} and C_{MICRO} were significantly lower than in patients with preserved CFVR (≥ 2.0) (respectively 0.8 [0.6-1.1] versus 1.1 [0.8-1.4], $p<0.001$, and 1.2 [0.9-1.6] versus 1.3 [1.0-1.8], $p=0.032$). C_{MICRO} was inversely correlated to HMR ($\rho=-0.52$, $p<0.001$).

EPICARDIAL CONDUCTANCE

C_{EPI} was significantly higher than C_{MICRO} with a median of 4.2 (2.1-8.0) cm/s/mmHg ($p<0.001$). C_{EPI} was significantly lower in vessels with $\geq 50\%$ DS, compared to vessels $<50\%$ DS (2.3 [1.2-4.7] versus 4.3 [1.9-8.5], $p=0.001$) and it was significantly lower in vessels with abnormal FFR (1.2 [0.7-2.5] versus 5.1 [2.8-9.2] in vessels below and above the FFR cut-off respectively, $p<0.001$). There was a positive correlation between C_{EPI} and FFR ($\rho=0.54$, $p<0.001$) and a negative correlation between C_{EPI} and HSR ($\rho=-0.65$, $p<0.001$). Vessels that were concordantly classified by FFR and HSR (280 [84%]) were used as the best possible reference population to establish the diagnostic efficiency of C_{EPI} . ROC curves indicated an optimal cut-off value of 1.69 (AUC 0.93) to characterise a significant epicardial stenosis with a sensitivity of 82% and a specificity of 93%. C_{EPI} demonstrated a higher AUC to determine a significant epicardial stenosis as compared to CFVR or overall conductance (Figure 4). The distribution of C_{EPI} in classification quadrants that are outlined by FFR and HSR is shown in Supplementary Figure 1. The effect of epicardial disease (assessed by C_{EPI}) on hyperaemic pressure, flow velocity (APV) and C_{MICRO} is shown in Figure 5A. The median of the ratio between C_{EPI} and C_{MICRO} was 3.19 (1.54-6.27). The optimal cut-off-value of the $C_{\text{EPI}}/C_{\text{MICRO}}$ ratio to identify ischaemia-generating stenoses was close to one (≤ 0.97) with a sensitivity of 67.5% and a specificity of 96.3% (AUC 0.90) (Figure 5B).

ZERO-FLOW PRESSURE

Supplementary Appendix 1 and Supplementary Figure 2 show zero-flow pressure results.

Discussion

In the present study, we demonstrated the feasibility of a combined haemodynamic assessment of the coronary circulation by performing a separate calculation of epicardial and micro diastolic vascular conductance. We found that: 1) C_{EPI} has a great efficiency to detect a clinically relevant stenosis; 2) C_{MICRO} is independent of stenosis severity, thus is a specific index of microvascular dysfunction; and 3) it is possible to obtain Pzf values by this technique. Using

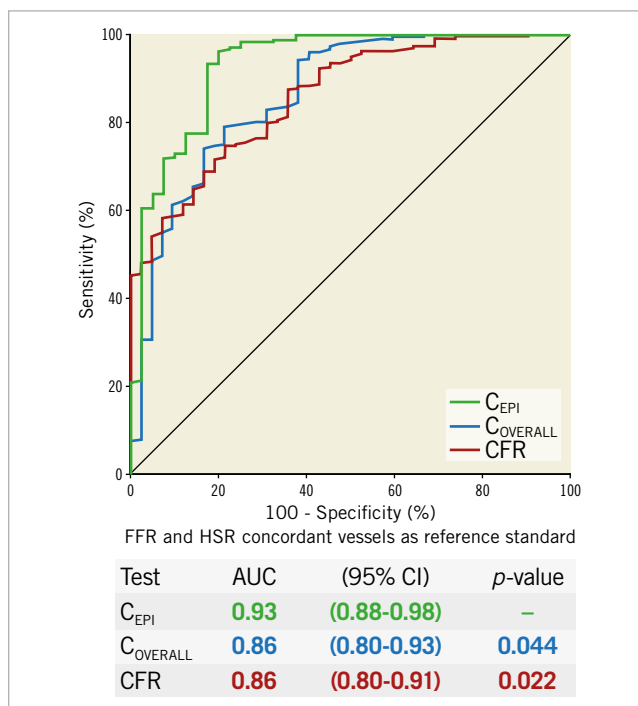


Figure 4. ROC curve of epicardial conductance against FFR and HSR. ROC curves of overall conductance and CFVR are similar and indicate combined microvascular and epicardial disease. There is significant improvement in area under the receiver operating curve of epicardial conductance, supporting its value in detecting clinically relevant obstructive disease. Vessels with concordant values of FFR (≤ 0.8) and HSR (≤ 0.8) are used to investigate the diagnostic efficiency of epicardial conductance. AUC: area under the curve; C_{EPI} : epicardial conductance; CFR: coronary flow reserve; C_{OVERALL} : overall conductance; FFR: fractional flow reserve; HSR: hyperaemic stenosis resistance

a comprehensive new method, it is possible to investigate simultaneously the status of the epicardial vessel and microcirculation separately, using the same units for both domains. In the next paragraphs, we discuss relevant aspects of this diagnostic approach.

CURRENTLY AVAILABLE METHODS TO ASSESS THE INTRACORONARY HAEMODYNAMICS OF THE CORONARY CIRCULATION

The current main role of coronary physiology in the catheterisation laboratory is to guide coronary revascularisation (primarily with FFR). A diagnosis of microvascular dysfunction is also desirable, as it has been demonstrated that it influences prognosis¹⁷. Therefore, an intracoronary diagnostic tool capable of providing information simultaneously on the presence of epicardial disease and microcirculatory dysfunction constitutes an unmet need in the assessment of IHD.

Assessment of the coronary microcirculation is performed predominantly with indices of vascular resistance (HMR and the index of microvascular resistance [IMR]), which are frequently influenced by the presence of epicardial stenosis. Consequently, current

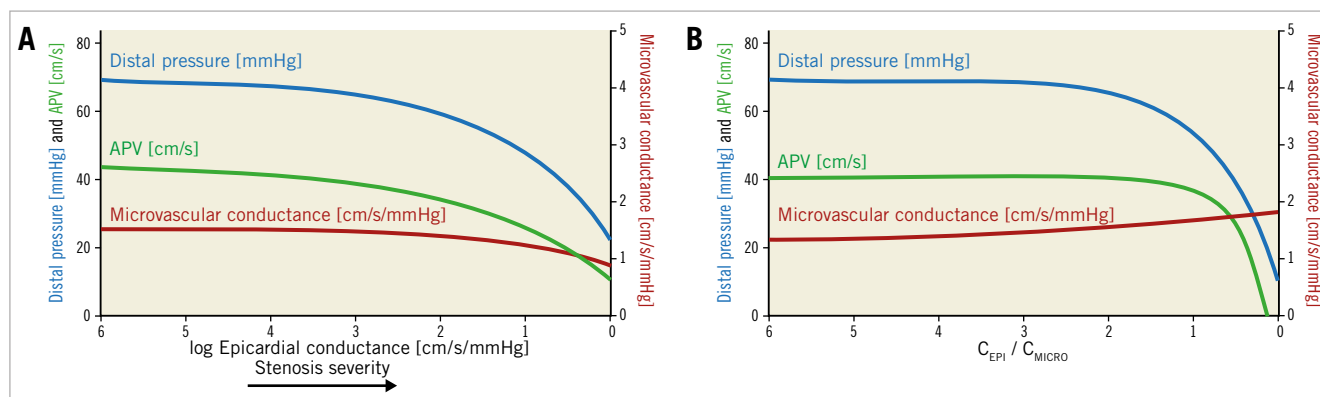


Figure 5. Effect of epicardial disease on distal pressure, coronary flow velocity and microvascular conductance. A) The panel indicates a marked decrease in intracoronary hyperaemic pressure and flow velocity around the values identified as the optimal cut-off value for epicardial conductance. Microvascular conductance is not affected until close to zero. B) The panel indicates a marked decrease in intracoronary hyperaemic pressure and flow velocity around the values identified as the optimal cut-off value (≤ 0.95) for the ratio between epicardial and microvascular conductance. This is when epicardial conductance becomes lower than microvascular conductance (ratio < 1). APV: average peak velocity; C_{EPI} : epicardial conductance; C_{MICRO} : microvascular conductance

epicardial and microvascular indices are expressed in different units (a dimensionless pressure ratio and resistance units, respectively). Using conductance, it is possible to compare the amount of epicardial and microvascular disease (same units for both domains) to determine the predominant domain causing myocardial ischaemia.

CONDUCTANCE: AN INTEGRAL APPROACH TO ASSESS BOTH EPICARDIAL AND MICROVASCULAR DOMAINS

Conductance provides an estimate of the maximal delivery of myocardial blood. As the maximal delivery of myocardial blood happens mostly during diastole¹⁸, we limited the interrogation to the mid-late diastolic phase. By doing so, measurements were obtained in the absence of fluctuations in extravascular compression (during systole) and capacitance (early diastole)¹⁹. We were encouraged by previous research from our group demonstrating that assessment of C_{MICRO} correlated well with documented structural remodelling of micro-vessels⁸.

The first challenge was to ascertain how separate calculation of C_{EPI} could be obtained. This was solved by deriving a mathematical solution from the electric analogue of the coronary circulation. The second challenge was to validate these findings in the absence of a single reference standard for the severity of epicardial disease. As FFR alone is influenced by the status of the microcirculation and we aimed for a specific epicardial index as reference standard, we opted for its combination with an additional intracoronary index, HSR²⁰, as the best approach in our data set to characterise clinically relevant epicardial disease.

EPICARDIAL CONDUCTANCE HAS A HIGH DIAGNOSTIC EFFICIENCY TO DETECT CLINICALLY RELEVANT EPICARDIAL DISEASE

As expected, we found a much higher conductance in the epicardial vessels (conductance vessels) without stenotic epicardial

disease than in the microcirculation. Below the established cut-off value of C_{EPI} , distal pressure and flow velocity steeply decrease. In other words, coronary disease becomes ischaemia-generating when C_{EPI} becomes lower than C_{MICRO} . Beyond that point, the microcirculation is no longer able to compensate for epicardial obstruction²¹. C_{EPI} had a remarkable power to identify clinically relevant stenoses, as judged by the concordance of two validated clinical indices^{20,22}.

MICROVASCULAR CONDUCTANCE IS INDEPENDENT OF STENOSIS SEVERITY

Mean values of C_{MICRO} in our data set are similar to those in previously published studies^{8,23}. We demonstrated that diastolic C_{MICRO} is independent of epicardial stenosis severity, as opposed to whole-cycle based CFVR, IMR and HMR^{4-6,24}. These prior studies, based on averaged whole-cycle pressure and flow velocity data, reported an increase in microcirculatory resistance in the presence of haemodynamically severe stenoses. More recent studies, which calculated microvascular indices from averaged mid and late diastole data, suggested that such a relationship results from the early diastolic or systolic phenomena²⁵. Our results fit well with the previously published work carried out by our group indicating that C_{MICRO} correlates better to structural microvascular changes compared to other microvascular indices⁸.

Limitations

While the quality of flow velocity tracings is key for the calculation of conductance, perfect Doppler signals are not always obtainable. In line with previous studies, coronary conductance could not be measured in around 25% due to suboptimal tracings^{23,26,27}. Corrections of pressure drift were made assuming that it resulted from deviation of Pd values (i.e., was caused by the wire pressure sensor). A limitation of our study was that we did not measure proximal flow to calculate

overall conductance, but instead we used the distal flow velocity. However, in the coronary vessels, flow velocity is kept constant due to proportionality between subtended myocardial mass and the coronary luminal diameter¹⁰. Of note, other indices such as HSR also use distal flow velocity to assess the severity of epicardial disease. Furthermore, we did not assess volumetric flow but rather Doppler flow velocity. However, flow velocity theoretically does not require correction for vessel diameter or subtended mass^{11,28,29}. FFR and HSR were used as the optimal reference standard to validate C_{EPI} in our study, but in future research the potential of coronary conductance should be tested against an independent reference standard (for myocardial flow) such as positron emission tomography. Finally, the acquisition of conductance was performed off-line in the absence of commercially available systems. Future developments in these dedicated software programs might obviate this limitation.

Conclusions

We now provide a new integral approach to assess the coronary circulation haemodynamically with separate assessment of epicardial and microvascular diastolic conductance. C_{EPI} has a high diagnostic accuracy to detect a clinically relevant stenosis and C_{MICRO} is a specific microvascular index independent of stenosis severity. The conductance ratio incorporates both the epicardial and microvascular domains and emerges as a promising index to detect patients with myocardial ischaemia, as demonstrated by a marked decrease in distal intracoronary pressure and flow velocity, which seems to be when C_{EPI} becomes lower than C_{MICRO} .

Impact on daily practice

Vascular conductance is a promising novel technique to assess the epicardial and microvascular domains separately. Further research may focus on the advantages (e.g., diastolic interrogation, simultaneous interrogation of epicardial and microvascular disease, both indices expressing the same units, the ratio between C_{EPI} and C_{MICRO} being used to determine myocardial ischaemia and Pzf perhaps informing on extravascular compression) that each of the indices of conductance may have in clinical practice. Most likely, the combined use of C_{EPI}/C_{MICRO} and C_{MICRO} will suffice to ascertain whether epicardial disease is functionally relevant, while also indicating whether a structural microcirculatory problem exists.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Calculation and distribution of zero-flow pressure.

Supplementary Figure 1. Distribution of epicardial conductance in vessels classified by stenosis severity indicated by FFR and HSR.

Supplementary Figure 2. Distribution of Pzf in vessels classified by stenosis severity indicated by FFR and HSR.

The supplementary data are published online at:

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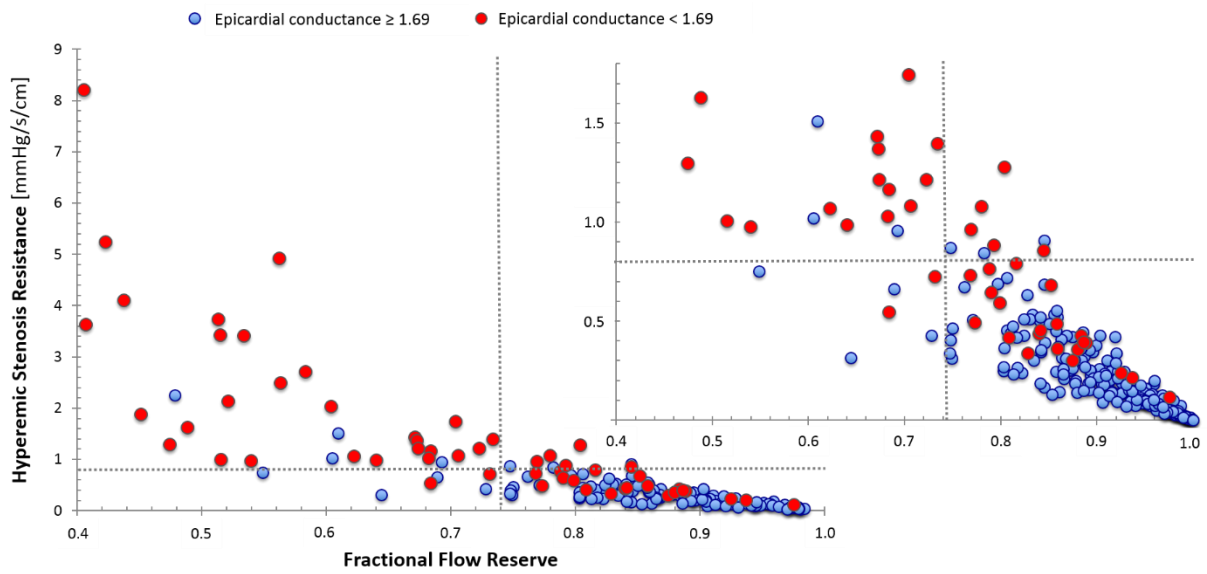
Supplementary data

Supplementary Appendix 1. Calculation and distribution of zero-flow pressure

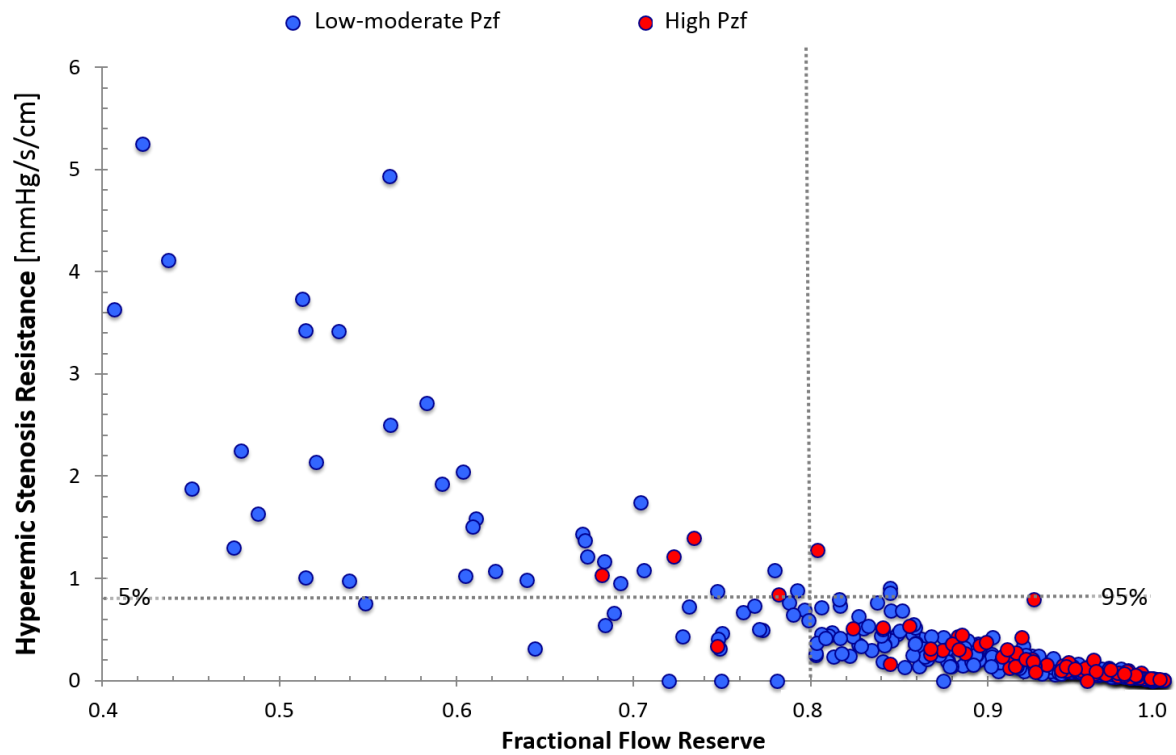
One of the advantages of this new approach is that it facilitates the estimation of Pzf values. Pzf is the distal pressure in the coronary arteries when theoretically intracoronary flow would be zero and is influenced by extravascular compression (e.g., interstitial haemorrhage, myocardial oedema or increased left ventricle end-diastolic pressure) and therefore has been mainly studied in the context of STEMI. Pzf is associated with clinical outcome in patients with STEMI. Previous research found that in the context of STEMI mean Pzf is around 45 mmHg, while in patients with stable disease much lower Pzf values have been reported. We demonstrated that elevated values of Pzf are predominantly present in vessels with FFR >0.8 (see results below). It has been proposed that the presence of Pzf requires a modification of the calculation of FFR, taking Pzf into account.

Calculation of Pzf was feasible in 401 vessels (75.1%) and was 28.89 ± 14.16 mmHg. Pzf was higher in the RCA compared to the LAD (33.41 ± 13.77 versus 27.53 ± 13.18 , $p=0.004$). Pzf was significantly higher in vessels with FFR >0.80 compared to vessels with FFR ≤ 0.8 (31.68 ± 13.52 versus 20.72 ± 14.11 , $p<0.001$). **Supplementary Figure 2** shows the distribution of Pzf in relation to FFR and HSR, in which the uppermost quartile (Q4 = Pzf >38.7) is highlighted with a significantly different between-group distribution ($p=0.028$). Almost all values of high Pzf (Q4) demonstrate an accompanying high FFR value. In only 5 vessels (5.9%) with an elevated Pzf was an FFR ≤ 0.8 found.

The exact role of Pzf in patients with stable coronary artery disease still needs to be evaluated further.



Supplementary Figure 1. Distribution of epicardial conductance in vessels classified by stenosis severity indicated by FFR and HSR. The optimal cut-off value is established with a receiver operating curve. Vessels with epicardial conductance below 1.69 are highlighted in red. The panel on the right represents a magnification of the panel on the left. The horizontal and vertical lines represent FFR (≤ 0.8) and HSR (≤ 0.8).



Supplementary Figure 2. Distribution of Pzf in vessels classified by stenosis severity indicated by FFR and HSR. High

Pzf is marked by red dots and represents the highest 25th percentile (38.7 mmHg). The horizontal and vertical lines represent FFR (≤ 0.8) and HSR (> 0.8). It becomes evident that elevated Pzf values are associated with FFR > 0.8 (95%).

FFR: fractional flow reserve; HSR: hyperaemic stenosis resistance; Pzf: zero-flow pressure