

# Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans

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## KEYWORDS

- absolute coronary blood flow
- absolute coronary resistance
- clinical research
- coronary circulation
- fractional flow reserve
- microvascular resistance
- other technique

## Abstract

**Background:** Absolute hyperaemic coronary blood flow (Q, in mL/min) and resistance (R, in Wood units [WU]) can be measured invasively by continuous thermodilution.

**Aims:** The aim of this study was to assess normal reference values of Q and R.

**Methods:** In 177 arteries (69 patients: 25 controls, i.e., without identifiable coronary atherosclerosis; 44 patients with mild, non-obstructive atherosclerosis), thermodilution-derived hyperaemic Q and total, epicardial, and microvascular absolute resistances ( $R_{tot}$ ,  $R_{epi}$ , and  $R_{micro}$ ) were measured. In 20 controls and 29 patients, measurements were obtained in all three major coronary arteries, thus allowing calculations of Q and R for the whole heart. In 15 controls (41 vessels) and 25 patients (71 vessels), vessel-specific myocardial mass was derived from coronary computed tomography angiography.

**Results:** Whole heart hyperaemic Q tended to be higher in controls compared to patients (668±185 vs 582±138 mL/min,  $p=0.068$ ). In the left anterior descending coronary artery (LAD), hyperaemic Q was significantly higher (293±102 mL/min versus 228±71 mL/min,  $p=0.004$ ) in controls than in patients. This was driven mainly by a difference in  $R_{epi}$  (43±23 vs 83±41 WU,  $p=0.048$ ), without significant differences in  $R_{micro}$ . After adjustment for vessel-specific myocardial mass, hyperaemic Q was similar in the three vascular territories (5.9±1.9, 4.9±1.7, and 5.3±2.1 mL/min/g,  $p=0.44$ , in the LAD, left circumflex and right coronary artery, respectively).

**Conclusions:** The present report provides reference values of absolute coronary hyperaemic Q and R. Q was homogeneously distributed in the three major myocardial territories but the large ranges of observed hyperaemic values of flow and of microvascular resistance preclude their clinical use for inter-patient comparison.

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## Abbreviations

<b>FFR</b>	fractional flow reserve
<b>IMR</b>	index of microcirculatory resistance
<b>LAD</b>	left anterior descending coronary artery
<b>LCX</b>	left circumflex coronary artery
<b>PET</b>	positron emission tomography
<b>Q</b>	flow
<b>R</b>	resistance
<b>RCA</b>	right coronary artery
<b>T</b>	temperature

## Introduction

Coronary blood flow is essential for proper myocardial function<sup>1,2</sup>. Microvascular resistance constantly matches coronary flow to the needs of the myofilaments<sup>3-5</sup>.

Fractional flow reserve (FFR) derived from pressure measurements<sup>6,7</sup> determines the contribution of epicardial stenoses to alterations of myocardial perfusion, and has therefore been recognised as the standard of reference to guide “revascularisation” of epicardial lesions<sup>8</sup>.

In contrast, assessing the coronary microcirculation requires measurements of microvascular resistances. The index of microcirculatory resistance (IMR)<sup>9</sup>, a bolus thermodilution-based technique, has been shown to be useful for predicting clinical outcome in patients immediately after an acute myocardial infarction<sup>10</sup>. It recently received a level IIa recommendation in the European Society of Cardiology Guidelines for the investigation of patients with suspected microvascular dysfunction and in patients with chronic coronary syndromes<sup>11</sup>. So far, there has been no direct invasive measurement tool to quantify the function of the microcirculation in absolute terms in humans. This is the main reason why there has been limited clinical interest in the study and the treatment of coronary microcirculatory dysfunction<sup>12</sup>.

We described and validated a method based on continuous thermodilution that enables the quantification of absolute coronary blood flow (expressed in mL/min) and absolute microvascular resistance (expressed in mmHg/L/min or Wood units [WU])<sup>13</sup>. Recent technical improvements have made this approach reproducible<sup>14</sup> and easy to implement in the catheterisation laboratory<sup>15,16</sup>. The accuracy of thermodilution-derived myocardial flow and resistance measurements was confirmed by comparison with [<sup>15</sup>O]H<sub>2</sub>O PET-derived flow and resistance<sup>17</sup>.

A necessary prerequisite for its clinical application is to define a range of normal values.

Accordingly, the goals of the present study were to establish ranges of absolute flow and resistance by continuous coronary thermodilution in normal individuals and in patients with mild, non-obstructive coronary atherosclerosis.

## Methods

The study was a prospective registry performed in two hospitals. The study protocol was approved by the institutional review boards.

## PATIENTS

Patients were included in one of two groups. Group 1 comprised individuals with normal coronary arteries (n=25). These individuals were considered to have a truly normal coronary circulation if they had a strictly normal coronary angiogram, normal left ventricular (LV) function, no valvular disease, an FFR >0.80 in all coronary arteries and, when available, a normal coronary computed tomography angiography (CTA) with an Agatston score of zero. These patients were referred to as “normals”.

Patients in Group 2 had mild, non-obstructive coronary atherosclerosis (n=44). Such patients were included if they had proven coronary atherosclerosis (either at CT or at coronary angiography, or both) but no focal stenosis more than 30% by visual estimation.

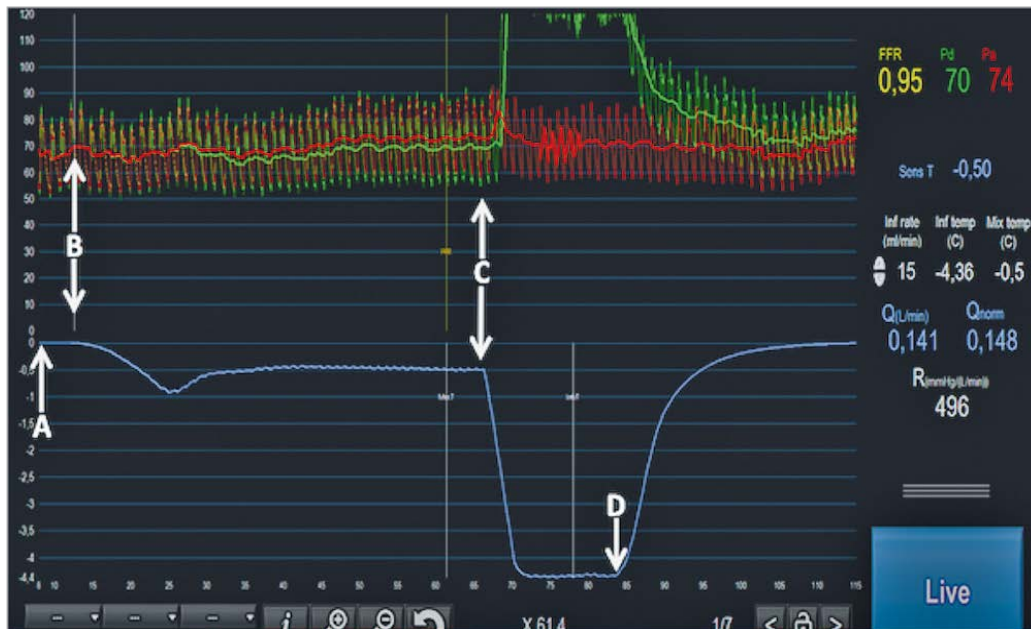
In 20 out of 25 normals and in 29 out of 45 patients with atherosclerosis, flow and resistance measurements were performed in all three major coronary arteries in case of a right dominant arterial system, or only in the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LCX) in case of a non-dominant right coronary artery (RCA). In these patients, flow and resistance of the whole heart could be assessed.

## CT SCANNING FOR CALCULATION OF MYOCARDIAL MASS

Forty patients (15 normals and 25 patients with mild atherosclerosis) underwent a coronary CT angiogram performed on a 256-slice scanner (Brilliance iCT [Philips Healthcare, Best, the Netherlands], or SOMATOM Flash [Siemens Healthineers, Forchheim, Germany]) which allowed calculation of the subtended myocardial mass for each coronary territory<sup>18,19</sup> by an independent core lab (HeartFlow Inc, Redwood City, CA, USA) blinded to the results of the invasive measurements. The methods have been detailed elsewhere<sup>20</sup>.

## CATHETERISATION

A 6 Fr arterial sheath was introduced into the radial or femoral artery, 100 U of heparin/kg of body weight was administered intravenously and intracoronary nitroglycerine (0.2 mg) was administered. A pressure/temperature sensor-tipped guidewire (PressureWire™ X; Abbott Vascular, Santa Clara, CA, USA) was zeroed, passed through the guiding catheter and, after proper equalisation with central aortic pressure, advanced into the distal part of the coronary artery. First, the FFR value was measured. Then, a dedicated monorail infusion catheter (RayFlow®; Hexacath, Paris, France) was connected to an infusion pump (Medrad Stellant; Medrad Inc, Warrendale, PA, USA), and flushed with saline at room temperature. The RayFlow catheter was advanced over the guidewire into the proximal segment of the artery to be measured. Details of the procedure have been described previously<sup>16</sup>. A typical tracing is shown in **Figure 1**. All coronary pressure and temperature tracings are wirelessly transmitted and analysed by a dedicated console equipped with a software (CoroFlow™; Coroventis, Uppsala, Sweden) that automatically calculates coronary blood flow (Q) and microvascular resistance ( $R_{\text{micro}}$ ).



**Figure 1.** Example of simultaneous pressures (upper tracings,  $P_a$  in red,  $P_d$  in green) and temperature recording (lower tracing, in blue) in a coronary artery. First, the temperature is “zeroed” (arrow A). This means that the body temperature prior to the measurement is considered as the zero. Soon after the start of the infusion of saline at room temperature (arrow B), the temperature measured in the distal artery ( $T$ ) decreases and stabilises at  $-0.50^\circ\text{C}$  below the zero line and the  $P_d$  starts to decrease slightly, indicating the presence of a higher coronary flow. Then, the sensor is pulled back (arrow C) and placed just in front of the inner holes of the RayFlow catheter (i.e., 2.5 mm distal to the marker on the RayFlow). This translates into a sharp decline of the temperature that stabilises at  $-4.36^\circ\text{C}$ . This value corresponds to the difference between body temperature and the saline at the location where saline enters the coronary artery ( $T_i$ ). Simultaneously, an increase in  $P_d$  is noted exceeding  $P_a$ . This is related to the fact that the pressure sensor is now located in the lumen of the infusion catheter and is influenced by the pressure delivered by the infusion pump. Finally, the infusion is stopped (arrow D), allowing both the pressure and the temperature to return to baseline. All relevant physiologic parameters (FFR,  $P_d$ ,  $P_a$ , infusion rate of saline, distal coronary temperature [ $T$ ], infusion temperature [ $T_i$ ], actual flow [ $Q$ ], normalised flow [ $Q_{norm}$ ] and minimal microvascular resistance [ $R_{micro}$ ]) are displayed instantaneously on the screen of any monitor by the CoroFlow software.

### CALCULATIONS OF FLOW AND RESISTANCE

Absolute volumetric coronary blood flow ( $Q$ ) can now be calculated and expressed in mL/min. This has been described previously and validated *in vitro*<sup>16</sup>, in animals<sup>13</sup> and in humans<sup>13</sup>. The simplified equation of continuous thermodilution-derived coronary blood flow ( $Q$ ) is as follows:

$$Q = 1.08 \times \frac{T_i}{T} \times Q_i$$

where  $Q_i$  is the infusion rate of saline through the RayFlow catheter in mL/min;  $T$  is the difference in temperature between the blood mixed with saline in the distal part of the artery and the blood temperature before infusion of saline, and  $T_i$  is the difference in temperature between saline when it enters the coronary circulation and the temperature of blood. The constant 1.08 relates to the difference between the specific heats and densities of blood and saline<sup>21</sup>.

Absolute resistances are calculated by analogy of Ohm's law as the ratio of pressure and flow and expressed in mmHg/L/min, or WU. As further explained in **Supplementary Appendix 1** and **Supplementary Figure 1-Supplementary Figure 3**, in each coronary artery the resistance can be calculated for the entire circulation

(**Figure 2**), i.e., the sum of the epicardial and microvascular compartments ( $R_{tot}$ ), and separately for the epicardial segment ( $R_{epi}$ ) and for the microcirculation ( $R_{micro}$ ) as follows (abbreviations as here above):

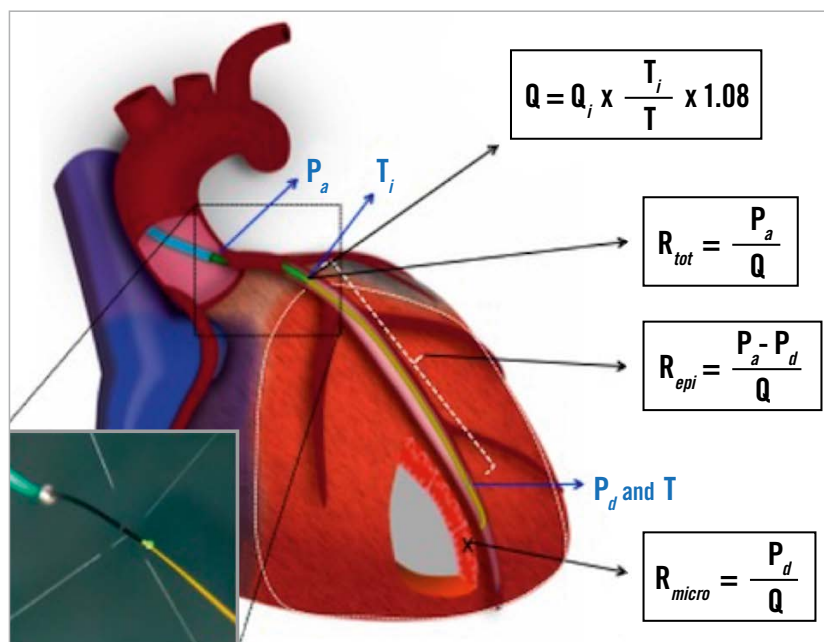
$$\text{Total coronary resistance: } R_{epi} = P_a / Q$$

$$\text{Epicardial resistance: } R_{epi} = (P_a - P_d) / Q$$

$$\text{Microvascular resistance: } R_{micro} = P_d / Q$$

### STATISTICAL ANALYSIS

Continuous variables with normal distribution are expressed as the mean  $\pm$  standard deviation and non-normally distributed variables as median and interquartile range. The normal ranges of  $Q$  and  $R$  are presented as the 5th and 95th percentiles. Categorical variables are expressed as counts and percentages. Continuous variables were compared using analysis of variance (ANOVA) or Kruskal-Wallis tests according to their distribution. Categorical variables were compared with the chi-square or Fisher's test, as appropriate. All analyses were performed using SPSS software, Version 24.0 (IBM Corp., Armonk, NY, USA) and figures were realised with Prism Mac 6.0h (GraphPad Software, La Jolla, CA, USA).



**Figure 2.** Comprehensive physiological framework of the entire coronary circulation. In the lower left corner, the infusion of saline through the dedicated catheter is shown.

## Results

### PATIENT CHARACTERISTICS

A total of 177 arteries in 69 patients (25 normals and 44 patients with mild atherosclerosis) were studied. The baseline characteristics are detailed in **Supplementary Table 1**. There were no complications associated with the procedure.

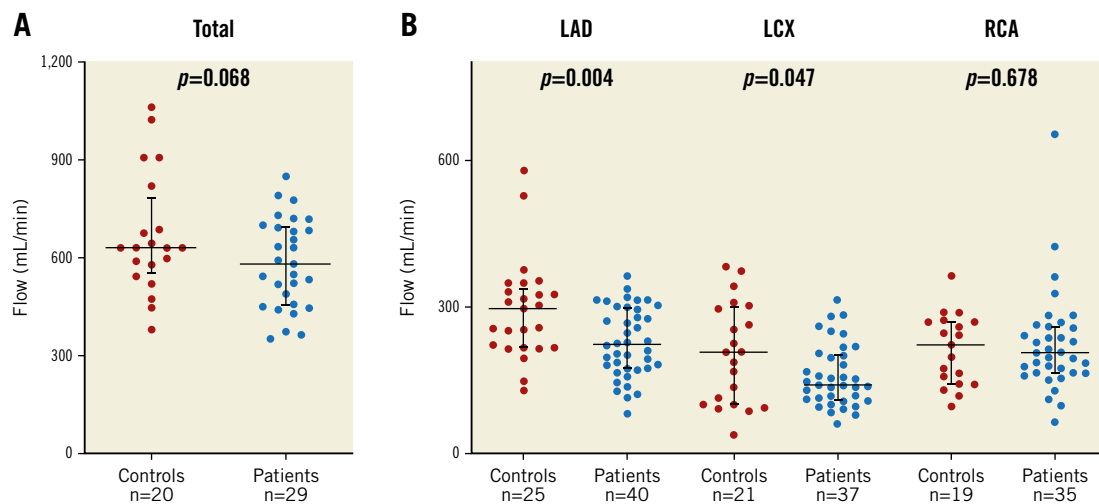
The values of FFR were higher in angiographically normal arteries than in mildly atherosclerotic arteries ( $0.95 \pm 0.03$  versus  $0.91 \pm 0.06$ , respectively,  $p=0.001$ ). These differences were driven mainly by the FFR values in the LAD.

### ABSOLUTE CORONARY FLOW VALUES

Details of all values of coronary flow in normals and in patients with mild atherosclerosis as stratified by artery are displayed in **Supplementary Table 2**.

Hyperaemic coronary flow for the whole heart, i.e., the sum of the flow in all three major coronary arteries, tended to be higher in normals than in patients with mild atherosclerosis ( $668 \pm 185$  mL/min versus  $582 \pm 138$  mL/min, respectively,  $p=0.068$ ) (**Figure 3A**).

Values of absolute coronary blood flow stratified by arteries are shown in **Figure 3B**. In the LAD, absolute hyperaemic



**Figure 3.** Absolute coronary artery blood flow. A) Individual values of whole heart coronary blood flow in normals and in patients with mild, non-obstructive atherosclerosis, i.e., sum of the flow in the LAD, the LCX and the RCA. B) Individual values of flow as stratified by coronary artery in normals and in patients with mild atherosclerosis.

flow was higher in normals than in patients with atherosclerosis ( $293\pm 102$  mL/min, versus  $228\pm 71$  mL/min, respectively,  $p=0.004$ ) as was the case in the LCX ( $p=0.047$ ). Large ranges of flow values were observed when stratified by vessel.

### TOTAL CORONARY RESISTANCE

Details are displayed in **Supplementary Table 2**.

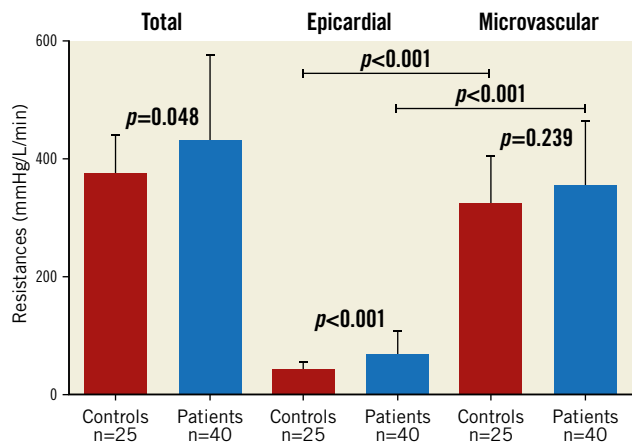
Hyperaemic total resistance for the whole heart was numerically, but not significantly, lower in normals than in patients with mild atherosclerosis ( $161\pm 45$  WU versus  $177\pm 48$  WU, respectively,  $p=0.244$ ) (**Figure 4A**). In the LAD, absolute total coronary resistance was lower in normals than in patients with mild atherosclerosis ( $379\pm 147$  WU versus  $462\pm 169$  WU, respectively,  $p=0.048$ ), while the difference did not reach statistical significance for the LCX and the RCA. Large ranges of hyperaemic flow and resistance values were observed when stratified by vessel (**Figure 4B**, **Supplementary Table 2**).

### EPICARDIAL AND MICROVASCULAR RESISTANCE

$R_{\text{tot}}$ ,  $R_{\text{epi}}$  and  $R_{\text{micro}}$  calculated for the LAD in normals and in patients with atherosclerosis are displayed in **Figure 5**.  $R_{\text{epi}}$  was significantly lower in normals than in patients with mild atherosclerosis ( $p<0.001$ ), which also reflects the higher FFR values measured in normals. There was no significant difference in  $R_{\text{micro}}$ . In both groups of patients,  $R_{\text{micro}}$  was markedly higher than  $R_{\text{epi}}$ .

### ABSOLUTE CORONARY FLOW AND RESISTANCE VALUES NORMALISED FOR MYOCARDIAL MASS (Supplementary Table 2)

In normals, after adjustment for the mass, the average values of Q observed in the three different vascular territories were similar ( $5.9\pm 1.9$ ,  $4.9\pm 1.7$ , and  $5.3\pm 2.1$  mL/min/g, for the LAD, the LCX and the RCA, respectively,  $p=NS$ ).  $R_{\text{micro}}$  was lower in the anterior wall than in the two other territories ( $15.5\pm 5.6$ ,  $20.6\pm 5.1$ , and  $21.7\pm 6.4$  mL/min/g, for the LAD, the LCX and the RCA, respectively,  $p<0.05$ ).

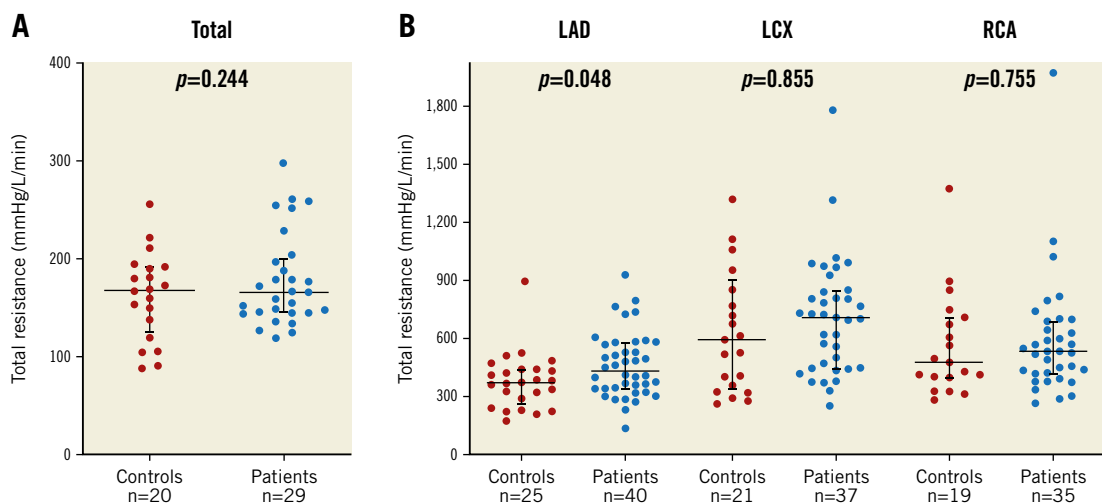


**Figure 5.** Total, epicardial, and microvascular resistances for the LAD in normals (red bars) and in patients with mild, non-obstructive atherosclerosis (blue bars) (mean $\pm$ SD).

## Discussion

### SUMMARY OF FINDINGS

The present report provides ranges of absolute values of hyperaemic Q and R assessed by continuous thermodilution in the coronary circulation in controls and in patients with mild, non-obstructive atherosclerosis. The main findings are as follows. 1) Hyperaemic flow of the whole heart is approximately 670 mL/min and total minimal microvascular resistance approximately 150 WU. 2) After normalisation for myocardial mass, absolute hyperaemic flow (mL/min/g) was similar among the three vascular territories. In contrast,  $R_{\text{micro}}$  was slightly lower in the LAD territory as compared to the LCX and RCA. 3) Total coronary hyperaemic Q was slightly lower and R slightly higher in patients with mild atherosclerosis as compared to controls. 4) Confirming earlier experimental studies by Gould<sup>22</sup> and by Chilian<sup>23</sup>, the major part of coronary resistance in humans is located in the microvasculature,



**Figure 4.** Absolute coronary artery total resistance. A) Whole heart total coronary resistance in normals and in patients with mild, non-obstructive atherosclerosis. B) Individual values of total resistance as stratified by coronary artery in normals and in patients with atherosclerosis (mean $\pm$ SD).

even during hyperaemia. 5) The wide range of hyperaemic flow and minimal  $R_{\text{micro}}$  precludes their use for inter-patient comparison, indicating that a more unequivocal index of  $R_{\text{micro}}$  is needed.

### THERMODILUTION-DERIVED FLOW

Absolute volumetric coronary flow (in mL/min) can be measured by continuous thermodilution using the hypothermic effect of saline at room temperature (negative temperature as compared to body temperature) as an indicator<sup>13</sup>. Recent technical improvements allow swift, safe, reproducible and accurate measurements<sup>14,16,24,25</sup>. These measurements can be obtained in the setting of coronary angiography and require a pressure/temperature sensor-tipped wire and a dedicated infusion catheter.

### NORMALS VERSUS PATIENTS WITH MILD ATHEROSCLEROSIS

Flow was slightly lower and resistance slightly higher in patients with mild atherosclerosis. At the level of the whole heart, these differences were not statistically significant as the sample size was underpowered to detect such differences. In addition, there was a large range of values of Q and R, as expected from the large variation in size of the coronary artery and the perfusion territory. In the LAD, hyperaemic flow was significantly larger in normals than in patients with atherosclerosis. Microvascular and epicardial resistances were higher in patients with mild atherosclerosis than in normals.

Our data suggest that epicardial atherosclerosis is not necessarily associated with the presence of microvascular dysfunction. Melikian et al<sup>26</sup> found a higher value of the IMR in patients with coronary artery disease compared to patients without coronary stenoses. However, a large overlap between IMR values of both groups was found, as was the case for absolute flow and resistance in the present study. These data and other data<sup>27</sup> suggest that, in many patients, a functional disconnect between epicardial atherosclerosis and microvascular dysfunction can be found.

### VARIABILITY OF ABSOLUTE HYPERAEMIC FLOW AND RESISTANCE

The main factor which may explain the large ranges in flow and resistance values is their dependence on myocardial mass. A unique advantage of positron emission tomography (PET)-derived flow and resistance is to express these measurements per unit of tissue mass (i.e., mL/min/g of tissue). Indeed, when adjusting Q and R for mass, similar values were found for the three different myocardial territories within the same patients. Yet, inter-individual values for Q and R, even when adjusted for mass, showed a considerable range<sup>28,29</sup>. In our study, the inter-individual variability of hyperaemic flow values was in the same order of magnitude as with PET. Therefore, it is likely that the large ranges of hyperaemic flow values also found in the present study do correspond to a naturally occurring large variability of normal hyperaemic values. Further confirming the hypothesis of a natural variation of hyperaemic myocardial perfusion, rather than that of measurement inaccuracies, Everaars et al found hyperaemic flow values ranging from approximately 50 to 450 mL/min in arteries

with mild atherosclerosis. These values of flow and microvascular resistance correlated very closely with the corresponding values obtained by PET. These data suggest that thermodilution-derived measurements are indeed accurate and therefore not responsible for this variability, and that hyperaemic coronary flow and microvascular resistance are highly variable from one individual to another. Driving coronary pressure is another factor that may explain the variability of flow values. During hyperaemia, flow is directly related to driving pressure<sup>6,30</sup>. The unique advantage of thermodilution-derived resistance measurements is to account for distal coronary pressure. This makes it possible to calculate separately microvascular resistance per territory even in the presence of decreased driving pressure. This is particularly important in patients with diffuse atherosclerosis in whom distal coronary pressure may be markedly lower than central aortic pressure, especially during hyperaemia.

### Limitations

The present study has a number of limitations. First, despite the fact that thermodilution-derived flow values have been validated *in vitro*<sup>16</sup>, in animals<sup>13</sup> and in humans<sup>17</sup>, hyperaemic perfusion values in the present study exceeded those derived from PET. Although speculative, several factors might play a role. Hyperaemia induced by saline infusion through the RayFlow catheter has been found to be consistently more potent than that induced by IV or IC adenosine<sup>15</sup>. In addition, it might be necessary to add the volume of saline that is infused as an indicator to the actual blood flow (even though in a fully dilated vascular system it is less likely to accommodate this additional volume). Also, the calculation of LV mass is based on a different principle than with PET. In the present study, we measured per territory mass derived from CT LV mass calculation, whereas with PET the measurement is performed per unit of volume of tissue which is then converted to mass using constant equations. The abovementioned factor may contribute to help to explain the relatively higher values of thermodilution-derived flow compared to PET.

Second, measurements were performed in arteries without focal stenoses, and should therefore not be extrapolated to territories perfused by significantly stenotic arteries. In practice, however, severe focal stenoses should be treated first before searching for microvascular disease as they often represent the main clinical problem for the patients.

Third, patients with atherosclerosis in the present study had a mild form of disease that might explain the absence of significant difference in  $R_{\text{micro}}$  between the groups. It is likely that, in more severe forms of atherosclerotic disease, the values of  $R_{\text{micro}}$  might have been higher.

Fourth, the presence of the RayFlow catheter in the proximal part of the artery tends to create a small gradient, especially during high coronary blood flow. Therefore, in this study, the actual flow has been slightly underestimated. The haemodynamic impact of the RayFlow catheter on the measured flow is corrected by the  $Q_{\text{norm}}$ , a metric that normalises the measured flow for the FFR.

Fifth, it should be realised that, when applying continuous thermodilution to measure absolute resistance,  $Q$  is measured at the tip of the infusion catheter, whereas  $P_d$  is measured more distal in the coronary artery. Therefore, small mistakes can be made in the calculation of resistances in case of atherosclerotic disease between the tip of the infusion catheter and the location where  $P_d$  is measured or when an epicardial stenosis is present in a side branch (Supplementary Figure 2).

## Conclusions

The present study is the first direct invasive quantification of total as well as vessel-specific coronary blood flow and resistance in the human heart. The data show that whole heart hyperaemic  $Q$  equals approximately 670 mL/min and tended to be higher in controls as compared to patients with mild, non-obstructive atherosclerosis. In normal individuals, total resistance of the coronary circulation was approximately 150 WU.  $Q$  was homogeneously distributed over the three territories.

The wide range of flow and microvascular resistance values – even after correction for myocardial mass – suggests that further correction for resting flow and resistance values is needed to allow meaningful inter-patient comparisons. However, the ease and the accuracy of invasive flow and resistance measurements make them particularly well suited for intra-patient clinical follow-up and to assess the effect of interventions on the coronary microvasculature within the same patient.

### Impact on daily practice

Using continuous coronary thermodilution to quantify absolute coronary flow, the present study provides, for the first time, ranges of reference values for hyperaemic coronary flow (in mL/min) and microvascular resistance (in Wood units). Overall flow was lower and microvascular resistance higher in patients with mild atherosclerosis than in normal individuals. Yet, the wide range of hyperaemic flow and microvascular resistance precludes their use for inter-patient comparison and indicates that a more unequivocal index of microvascular resistance is needed.

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## Conflict of interest statement

S. Fournier reports personal fees from Bayer and CathWorks. B. De Bruyne reports grants from Abbott, Boston Scientific, and Biotronik AG, personal fees from Abbott, Opsens, and Boston Scientific, and other from Siemens, GE, Bayer, Philips, HeartFlow, Edwards Lifesciences, and Ceyliad, during the conduct of the study. C. Collet reports grants from HeartFlow, Abbott Vascular, Biosensors, and Pie Medical, and consultancy fees from Abbott

Vascular, HeartFlow, Opsens and Philips. He serves as a member of the advisory board of Abbott Vascular, Pie Medical and Opsens. N. Pijls reports grants from Abbott, and Hexacath, personal fees from Abbott, Opsens, GE, and Biosensors, and other from GE, Philips, HeartFlow, and ASML, during the conduct of the study. The other authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Appendix 1.** Additional theoretical considerations on coronary flow and resistance.

**Supplementary Figure 1.** General considerations.

**Supplementary Figure 2.** The situation of side branches with a normal coronary artery and with diffusely diseased coronary arteries.

**Supplementary Figure 3.** A simplified coronary arterial circulation represented as three parallel conduits.

**Supplementary Table 1.** Patient characteristics.

**Supplementary Table 2.** Mean±standard deviation and median values (percentiles 5%-95%) of FFR, flow and resistances as stratified by artery.

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## Supplementary data

### Supplementary Appendix 1. Additional theoretical considerations on coronary flow and resistance

#### *Calculation of absolute blood flow (Q) and resistance (R) in the coronary circulation*

Absolute blood flow is calculated by the equation

$$Q = 1.08 \times (T_i / T) \times Q_i \quad (\text{Equation 1})$$

where  $Q_i$  represents the infusion rate of saline,  $T_i$  the temperature of the saline at the tip of the infusion catheter (where it enters into the coronary artery) and  $T$  the temperature of the completely mixed blood and saline in the distal coronary artery at the location of the pressure/temperature sensor. Complete and instantaneous mixing of blood and the “indicator” is a prerequisite of the general thermodilution theory.

$Q$  is expressed in ml/min.  $T$  is expressed in °C relative to normal blood temperature. In other words, if normal blood temperature before starting the measurement equals 37°C and  $T_i$  equals 32°C,  $T_i$  equals -5°C.

Absolute resistances are calculated by analogy of Ohm’s law as the ratio of pressure and flow and expressed in mmHg/L/min or Wood units.

In the coronary circulation, the resistance can be calculated separately for the entire coronary circulation ( $R_{\text{tot}}$ ), the epicardial segment ( $R_{\text{epi}}$ ), and the dependent microcirculation ( $R_{\text{micro}}$ ) as follows (**Supplementary Figure 1**):

Total coronary resistance:  $R_{\text{tot}} = P_a / Q \quad (\text{Equation 2})$

Epicardial resistance:  $R_{\text{epi}} = (P_a - P_d) / Q \quad (\text{Equation 3})$

Microvascular resistance:  $R_{\text{micro}} = P_d / Q \quad (\text{Equation 4})$

where  $P_a$  is mean aortic pressure as recorded by the guiding catheter and  $P_d$  is mean distal coronary pressure as recorded by the pressure wire.

A few remarks should be made to understand what the different resistances mean in different physiologic and pathologic situations.

1. **Flow and resistance in relation to the position of the infusion catheter**

Flow and resistance refer to the particular coronary artery and its dependent myocardial territory just distal to the position of the infusion catheter, i.e., flow and resistance distal to the tip of the RayFlow catheter.

In other words, if the tip of the RayFlow catheter is in the very proximal part of the left anterior descending coronary artery (LAD), flow refers to maximum flow in the LAD (including its side branches). Epicardial resistance refers to minimal resistance of the epicardial artery between the tip of the RayFlow catheter and the pressure/temperature sensor in the distal part of the artery. Microvascular resistance refers to minimal resistance of all myocardium belonging to the LAD and all side branches distal to the tip of the RayFlow catheter, i.e., the complete anterior wall in case that the RayFlow catheter is positioned in the very proximal LAD artery.

If one is interested in follow-up of flow and resistance within one patient such as, for example, an infarcted area after mid-LAD occlusion and stenting, the tip of the infusion catheter should be positioned just within the stent placed during PCI. In that case, flow and microvascular resistance of the infarct area are obtained.

2. **Influence of the infusion catheter on proximal pressure**

If the infusion catheter is located very proximally, no or very little pressure drop is present between  $P_a$  and the tip of the infusion catheter.

However, if the infusion catheter is positioned more distally within the coronary artery and in particular in case of diffuse disease (e.g., because one is specifically interested in that distal territory only), the pressure at the tip ( $P_m$ ) might be lower than  $P_a$ .

In that case,  $P_m$  can be measured by the pressure wire during the pullback recording to the tip of the infusion catheter and  $R_{epi}$  is given by  $(P_m - P_d)/Q$ .

Of note,  $R_{\text{micro}}$  is not affected and is still represented by  $P_d/Q$  as explained below.

3. **Focal obstructive epicardial disease**

Interest in microvascular (dys)function typically applies when angina is present in the absence (INOCA) - or after removal - of significant focal epicardial disease. When focal obstructive coronary artery stenoses are present, reflected by an  $\text{FFR} \leq 0.80$ , it is recommended, and conceptually sound, to treat the epicardial obstructions first, before flow and resistance are measured. This facilitates the interpretation of flow and resistance as will be clarified below.

4. **Diffuse disease and side branches**

The equation  $R_{\text{micro}} = P_d / Q$  (Equation 4) is valid under both physiologic and pathologic circumstances and its value refers to all myocardial territory (including side branches) distal to the tip of the infusion catheter. This can be understood as follows:

**Supplementary Figure 1.** General considerations.

In general:  $P_m / Q = (R_{\text{epi}} + R_{\text{micro}})$

$$\text{or:} \quad R_{\text{micro}} = P_m / Q - R_{\text{epi}} \quad (\text{Equation 5})$$

4A. *Completely normal artery:*

$$R_{\text{epi}} \approx 0 \quad \text{and} \quad P_m \approx P_a$$

$$\text{Therefore: } R_{\text{micro}} = P_d / Q$$

4B. *Diffuse disease:*

$$R_{\text{epi}} = (P_m - P_d) / Q = P_m / Q - P_d / Q$$

$$R_{\text{micro}} = P_m / Q - R_{\text{epi}} \quad (\text{according to Equation 5})$$

$$= P_m / Q - (P_m / Q - P_d / Q) = P_d / Q$$

$$\text{Therefore: } R_{\text{micro}} = P_d / Q$$

4C. *Side branches:*

Side branches do not influence calculation of  $R_{\text{micro}}$  assuming that there is no epicardial disease or that this disease is homogeneously distributed.

**Supplementary Figure 2.** The situation of side branches with a normal coronary artery and with diffuse diseased coronary arteries.

- *Side branches and strictly normal coronary arteries:*

In this case, the differences between  $P_m$ ,  $P_{d1}$  and  $P_{d2}$  are negligible and  $P_m$ ,  $P_{d1}$  and  $P_{d2}$  are assumed to be equal.

$Q_1$  and  $Q_2$  represent flow and  $R_1$  and  $R_2$  represent epicardial resistance in the main branch and the side branch, respectively.

$$R_{\text{epi}} = \frac{R_1 \times R_2}{R_1 + R_2} \quad (\text{law of parallel resistance})$$

$$= \frac{(P_m - P_d) / Q_1 \times (P_m - P_d) / Q_2}{(P_m - P_d) / Q_1 + (P_m - P_d) / Q_2}$$

$$= (\text{after algebraic transformation}) \quad \frac{P_m - P_d}{Q_1 + Q_2} = \frac{P_m - P_d}{Q} = \frac{P_m}{Q} - \frac{P_d}{Q}$$

$$R_{\text{micro}} = P_m / Q - R_{\text{epi}} \quad (\text{according to Equation 5})$$

In a similar way, it can be demonstrated that epicardial resistance ( $R_{\text{epi}}$ ) for a particular territory is always presented by  $(P_a - P_d) / Q$

$$\text{Therefore: } R_{\text{micro}} = P_m / Q - (P_m / Q - P_d / Q) = P_d / Q$$

- *Side branches and diffusely diseased coronary arteries:*

Same calculation as above, presuming that disease is homogeneously distributed. In that case,  $P_m$  will be slightly higher than  $Pd_1$  and  $Pd_2$  resulting in slight underestimation of the resistance.

- *Side branches with a focal narrowing:*

If the epicardial disease in a large side branch is completely different from the main branch (e.g., there is a tight focal stenosis in the side branch but not in the main branch or there is a tight focal stenosis in the main branch distal to the take-off of the side branch), the measurements need to be performed separately for the large side branch with the tip of the infusion catheter in the proximal part of that large side branch and the pressure sensor in its distal part. This will rarely be the case in clinical practice.

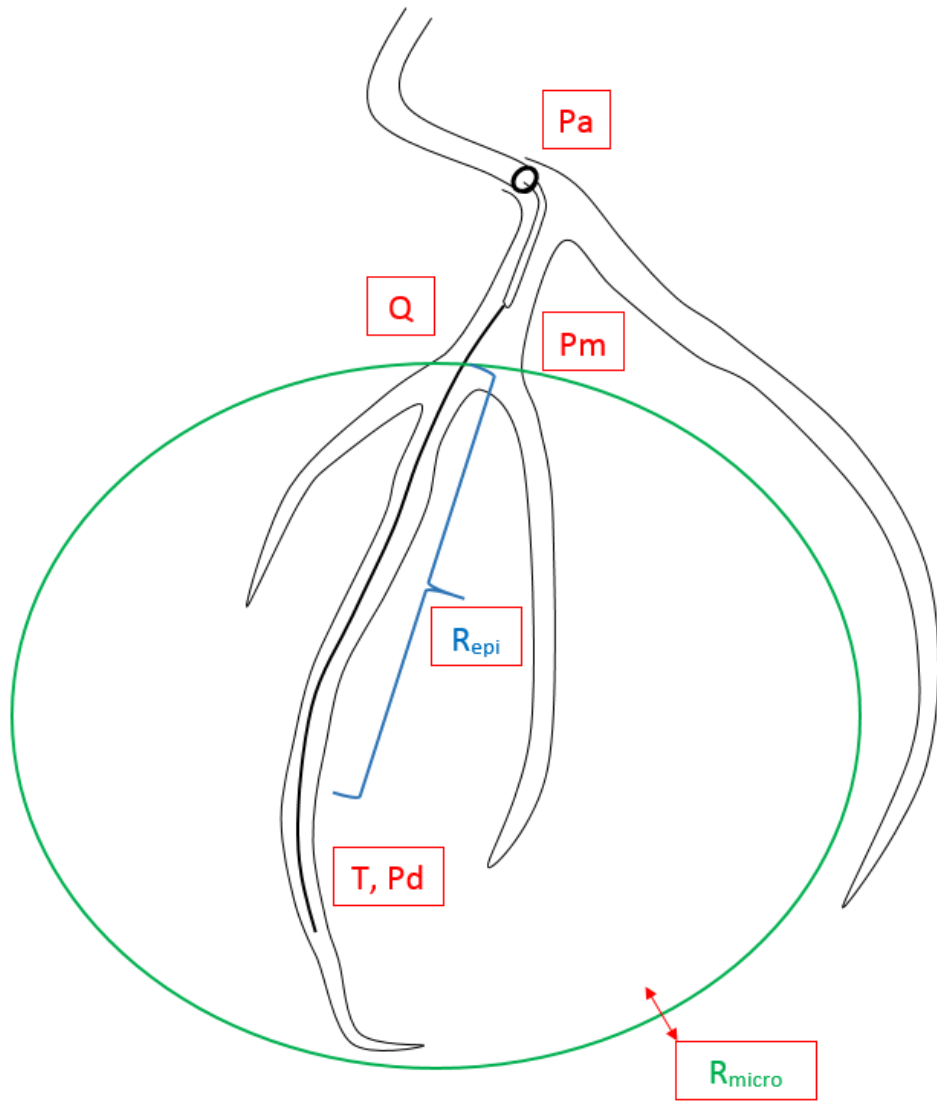
## 5. Calculations of the resistances of the whole heart

A simplified coronary arterial circulation can be represented as three parallel conduits (**Supplementary Figure 3**).

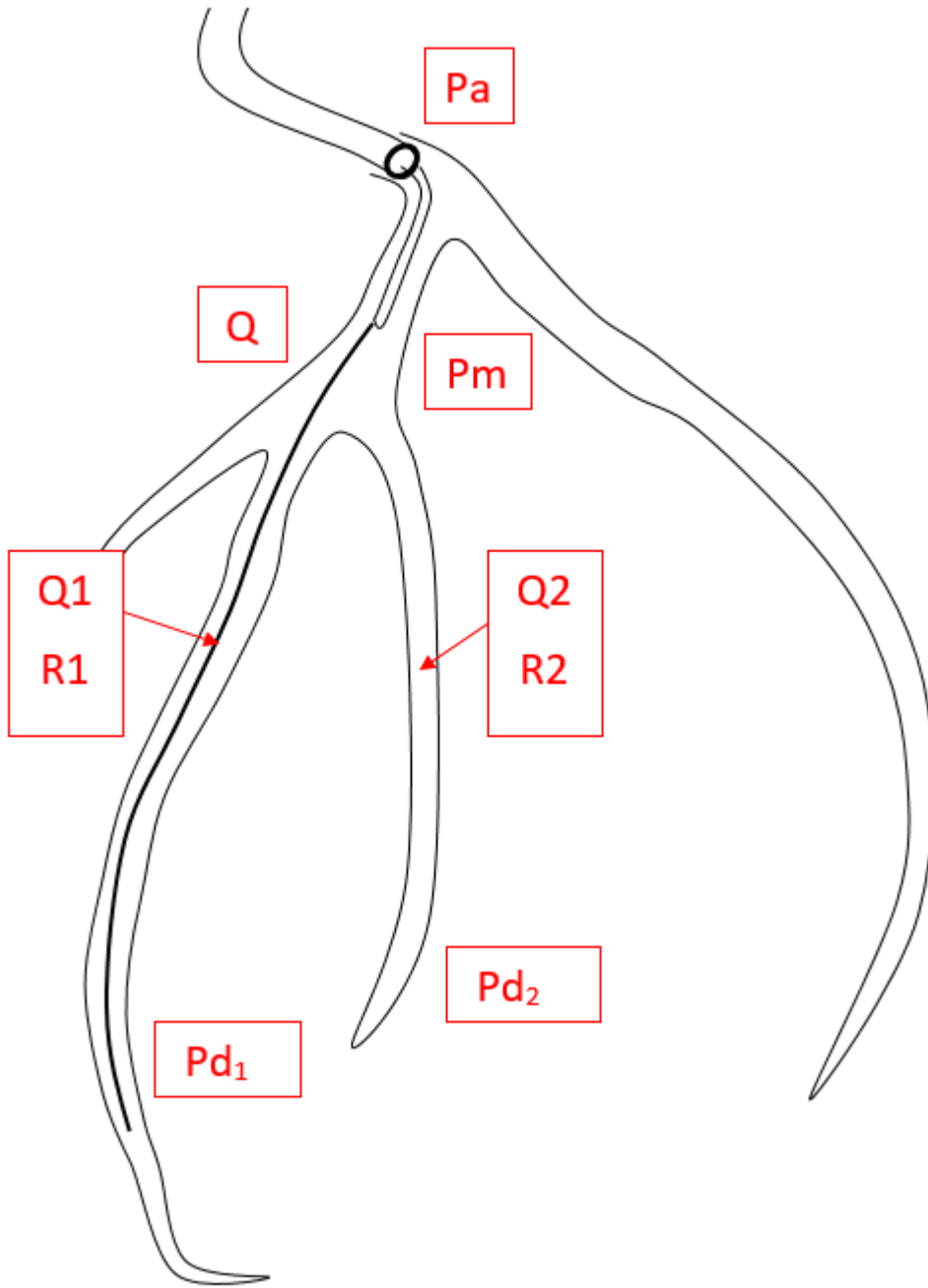
Each of these conduits consists of two resistances: the epicardial ( $R_{epi}$ ) and the microvascular resistance ( $R_{micro}$ ). Since these resistances are connected in series the replacement resistance ( $R_{tot,artery}$ ) of each of the three coronary arteries is equal to  $R_{epi} + R_{micro}$ . Therefore, the replacement resistance of the whole cardiac arterial coronary circulation can be calculated according to the law of parallel resistances as:

$$1/R_{whole\ heart} = 1/R_{tot,LAD} + 1/R_{tot,CX} + 1/R_{tot,RCA}$$

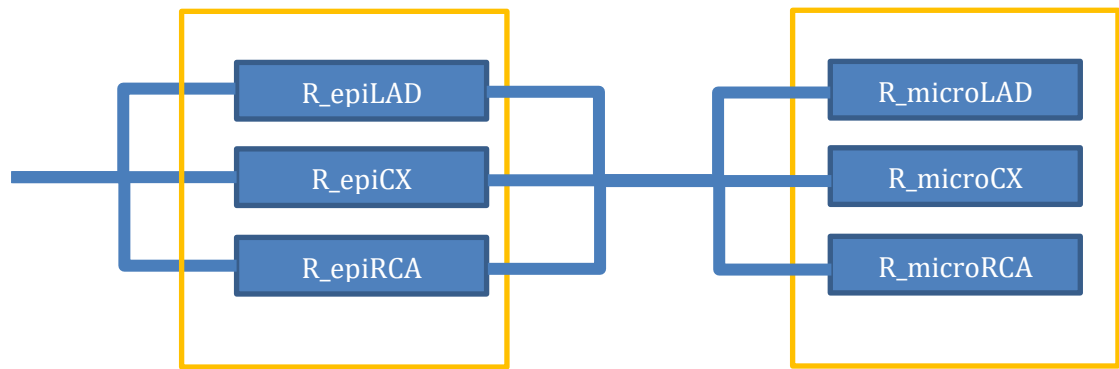
To calculate the replacement resistance for both the epicardial and microvascular resistances separately using the parallel resistance equation is only possible if pressures distal to the epicardial resistances are all equal. Only in this case the circulation could be represented as if these were connected as indicated in the figure here above. Therefore, the separation between  $R_{epi}$  and  $R_{micro}$  should only be performed per vessel.



**Supplementary Figure 1.** General considerations.



**Supplementary Figure 2.** The situation of side branches with a normal coronary artery and with diffuse diseased coronary arteries.



**Supplementary Figure 3.** A simplified coronary arterial circulation represented as three parallel conduits.



**Supplementary Table 1. Patient characteristics.**

	<b>Controls N=25</b>	<b>Mild atherosclerosis N=44</b>	<b>p- value</b>
Male gender, n (%)	9 (36)	22 (52.4)	0.19
Age, years, mean±SD	56.6±10.5	59.8±9.4	0.21
Height, mean±SD	1.71±0.1	1.71±0.1	0.65
Weight, mean±SD	79.8±13.5	82.5±13.6	0.42
BMI, mean±SD	27.46±4.91	27.91±3.62	0.33
<b>Risk factors</b>			
Hypertension, n (%)	4 (16)	12 (27.3)	0.52
Current smoking, n (%)	1 (4)	8 (18.6)	0.09
Diabetes mellitus, n (%)	3 (11.5)	2 (4.7)	0.26
Dyslipidaemia, n (%)	10 (40)	16 (38.1)	0.73
Family history, n (%)	9 (36)	11 (25.6)	0.40
Peripheral artery disease, n (%)	0 (0)	1 (2.4)	0.54
<b>Medication</b>			
Aspirin, n (%)	10 (40)	22 (52.4)	0.33
Antiplatelets, n (%)	3 (12)	10 (24.4)	0.22
Beta-blocking agents, n (%)	5 (20)	13 (31)	0.33
RAAS inhibitor, n (%)	4 (16)	11 (26.2)	0.33
Statin, n (%)	11 (44)	30 (71.4)	0.03
Nitrates, n (%)	1 (4)	9 (21.4)	0.05
<b>Left ventricular ejection fraction</b>			
<35%	0 (0)	0 (0)	0.64
35-50%	0 (0)	1 (2.4)	
>50%	25 (100)	43 (97.6)	

**Supplementary Table 2. Mean±standard deviation and median values (percentiles 5%-95%) of FFR, flow and resistances as stratified by artery.**

Invasive measurements		Controls N=25			Atherosclerosis N=44		
		LAD	Cx	RCA	LAD	Cx	RCA
<b>Pa</b>	Mean±SD	96±13	103±1 2	100±1 3	91±14	96±15	89±14
	Median (5-95)	96 (78-114)	100 (82-119)	103 (75-117)	93 (59-113)	100 (65-119)	88 (57-118)
<b>Pd</b>	Mean±SD	89±12	99±12	97±12	78±13	92±15	83±15
	Median (5-95)	87 (74-110)	98 (79-114)	99 (76-117)	81 (51-96)	94 (63-113)	83 (53-117)
<b>FFR</b>	Mean±SD	0.92±0.02	0.96±0.04	0.96±0.03	0.85±0.03	0.95±0.03	0.93±0.06
	Median (5-95)	0.93 (0.88-0.94)	0.97 (0.88-1.00)	0.96 (0.92-0.99)	0.86 (0.82-0.89)	0.96 (0.90-1.00)	0.94 (0.86-1.00)
<b>Q (mL/min)</b>	Mean±SD	293±10 2	204±10 4	197±63	228±71	160±64	189±65
	Median (5-95)	297 (149-528)	208 (87-374)	207 (78-275)	224 (119-329)	141 (80-284)	180 (81-317)
<b>Q<sub>norm</sub> (mL/min)</b>	Mean±SD	330±10	220±10	210±7 0	280±9 0	180±7 0	210±7 0
	Median (5-95)	330 (160-570)	258 (170-359)	220 (100-360)	270 (160-410)	160 (90-320)	200 (100-360)
<b>R<sub>epi</sub> (WU)</b>	Mean±SD	43±23	63±78	48±60	83±41	74±78	59±56
	Median (5-95)	44 (15-81)	36 (7-198)	30 (0-269)	70 (36-171)	47 (5-279)	38 (5-178)
<b>R<sub>micro</sub> (WU)</b>	Mean±SD	336±1 34	626±3 83	515±2 24	379±1 47	632±2 65	531±2 77
	Median (5-95)	325 (194-470)	549 (267-1,250)	417 (246-1,103)	356 (204-624)	617 (288-1,306)	479 (265-1,009)
<b>R<sub>total</sub> (WU)</b>	Mean±SD	379±1 47	689±4 45	563±2 68	462±1 69	707±3 00	589±3 07

	Median (5-95)	373 (209- 525)	593 (277- 1,319)	477 (283- 1,372)	431 (253- 780)	709 (330- 1,315)	533 (288- 1,101)
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CT data		Controls N=15			Atherosclerosis N=25		
<b>Myocardial mass (g)</b>	Mean±SD	50±12.9	35.9±16.4	48.7±15.9	52.2±17.5	36.4±13.5	46.5±17.8
	Median (5-95)	48.5 (34.7-70.9)	32.3 (15.4-60.7)	47.4 (30-73)	49.3 (32.7-78.1)	33.2 (15.4-60.7)	41.4 (24.7-75.7)
<b>Invasive measurements adjusted for myocardial mass in g as derived from CT</b>		<b>Controls N=15</b>			<b>Atherosclerosis N=25</b>		
<b>Q (mL/min/g)</b>	Mean±SD	5.9±1.9	4.9±1.7	5.3±2.1	4.7±1.3	4.7±2	5.2±1.4
	Median (5-95)	5.2 (3.3-8.9)	4.5 (3.3-8.2)	5.1 (3-8.8)	4.7 (2.6-6.7)	4 (2.7-8.3)	5.1 (3-7.4)
<b>R<sub>micro</sub> (WU x kg)</b>	Mean±SD	15.5±5.6	20.6±5.1	21.7±6.4	17.4±6.9	20.7±8.1	22.1±8.4
	Median (5-95)	14.6 (9.2-25.7)	22.8 (12.4-26)	22.9 (12.8-30.4)	16.4 (9.4-31.7)	20 (9.7-32.3)	19 (15.3-41.8)

The lower part of the table displays the myocardial mass as derived from coronary computed tomography angiography and the values of flow and microvascular resistance adjusted for the corresponding values of myocardial mass.

CT: coronary computed tomography angiography; Q: hyperaemic flow; Q<sub>norm</sub>: hyperaemic flow corrected for the FFR; R<sub>epi</sub>: epicardial resistance; R<sub>micro</sub>: microvascular resistance; R<sub>total</sub>: total coronary resistance