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Absolute coronary blood flow measurement and microvascular resistance in ST-elevation myocardial infarction in the acute and subacute phase[☆]

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ABSTRACT

Background/Purpose: In a number of patients with acute myocardial infarction (AMI), myocardial hypoperfusion, known as the no-reflow phenomenon, persists after primary percutaneous intervention (PPCI). The aim of this study was to evaluate the feasibility and safety of a new quantitative method of measuring absolute blood flow and resistance within the perfusion bed of an infarct-related artery. Furthermore, we sought to study no-reflow by correlating these measurements to the index of microvascular resistance (IMR) and the area at risk (AR) as determined by cardiac magnetic resonance imaging (CMR).

Methods: Measurements of absolute flow and myocardial resistance were performed in 20 patients with ST-segment elevation myocardial infarction (STEMI), first immediately following PPCI and then again after 3–5 days. These measurements used the technique of thermodilution during a continuous infusion of saline. Flow was expressed in ml/min per gram of tissue within the area at risk.

Results: The average time needed for measurement of absolute flow, resistance and IMR was 20 min, and all measurements could be performed without complication. A higher flow supplying the AR correlated with a lower IMR in the acute phase. Absolute flow increased from 3.14 to 3.68 ml/min/g ($p = 0.25$) and absolute resistance decreased from 1317 to 1099 dyne.sec.cm-5/g ($p = 0.40$) between the first day and fifth day after STEMI.

Conclusions: Measurement of absolute flow and microvascular resistance is safe and feasible in STEMI patients and may allow for a better understanding of microvascular (dys)function in the early phase of AMI.

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1. Introduction

In acute myocardial infarction, early restoration of blood flow to the jeopardized myocardium is of paramount importance to limit infarct size and obtain a favorable long-term outcome. Primary percutaneous coronary intervention (PPCI) is the treatment of choice for reestablishing epicardial blood flow in patients with ST-segment elevation myocardial infarction (STEMI) [1,2]. Despite achievement of epicardial coronary artery reperfusion in approximately 90% of all patients, a number of these patients experiences persistent myocardial hypoperfusion due to moderate or severe microvascular dysfunction, also referred to as the “no-reflow” phenomenon [3–6]. In 1974, Kloner et al. described this phenomenon in dogs and showed that, after the temporary occlusion of a coronary artery, subendocardial perfusion defects were detectable and persistent after 90 min of occlusion [7]. Failure of reflow

was associated with extensive capillary damage and myocardial cell swelling, leading to injury of the myocardial microvasculature.

The pathogenesis of no-reflow has not been elucidated completely and seems to be complex and multifactorial. Microvascular thromboembolism, spasm, intramyocardial edema and inflammatory responses of the myocardium with neutrophil plugging of the capillaries are all suggested to be responsible for this condition. It is well known that in patients in whom no or poor reflow occurs, prognosis is poor and more severe left ventricular dysfunction can be expected in comparison to those patients in whom microvascular reperfusion after PPCI is restored [6,8]. Therefore, knowledge about the actual state of the microvasculature and myocardial perfusion shortly after PPCI is important from a prognostic point of view.

Moreover, if microvascular reperfusion is still limited immediately after myocardial infarction, but recovers quickly in the days thereafter, it might be beneficial for long-term prognosis [8]. Lastly, knowledge about microvascular reperfusion in the acute phase might be important with respect to choice of adjunct mechanical or medical therapy, such as intra aortic balloon pumping (IABP), glycoprotein IIb/IIIa inhibitors or continuation of nitroglycerine.

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Assessment of microvascular perfusion and function has so far been difficult and hampered by a number of methodological and technical shortcomings. Furthermore, measurement of absolute blood flow in the infarcted area and true quantitative calculation of absolute resistance in acute MI has never been performed.

Recently, a new invasive technique for measuring absolute coronary blood flow and absolute myocardial resistance has been developed for patients with stable coronary disease [9]. This technique is based upon thermodilution using a continuous infusion of a low amount of saline through a microcatheter positioned selectively in a coronary artery. This technique is precise and not operator-dependent [9,10]. Measuring absolute blood flow and resistance has no meaning by itself as long as the distribution territory is unknown. Also, it is difficult to compare flow and resistance among territories, not to mention among patients. However, if the area of interest is the dependent myocardial territory of the occluded coronary artery, this technique makes it possible to compare absolute flow (ml/min) in STEMI patients between the moment immediately after epicardial reperfusion by PPCI and the recovery phase a few days later, with potential implications for treatment. Because the sensor measuring absolute blood flow by continuous infusion methodology simultaneously measures distal coronary pressure, absolute minimal resistance can be calculated in $\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$, as shown before in experimental studies and in humans with stable coronary artery disease [9]. This quantitative measurement of flow and resistance is accurate and offers advantages over qualitative and indirect measures of resistance in STEMI, such as flow velocity-based indices or IMR [11,12].

Consequently, the purpose of the present study was to evaluate the feasibility and safety of absolute blood flow measurement and resistance in STEMI patients, both in the acute and subacute phases. Furthermore, we aimed to correlate this method of flow measurement to IMR, the existing, non-quantitative, invasive standard method for detecting microvascular dysfunction.

2. Material and methods

2.1. Patient selection and inclusion criteria

STEMI patients <75 years of age admitted for PPCI with a total ST-segment deviation of more than 10 mm were eligible if they presented within 12 h of symptom onset and had a culprit lesion in the proximal or mid segment of a coronary artery whose reference diameter was ≥ 3.0 mm by visual estimation. Patients with previous myocardial infarction in the culprit area or with previous bypass surgery were excluded. Other exclusion criteria were cardiogenic shock, inability to obtain femoral access to the arterial circulation, tortuous coronary arteries, complex or long-lasting PPCI, inability to understand and give informed consent, severe concomitant disease or conditions with a life expectancy of less than one year, other known myocardial diseases such as cardiomyopathy or left ventricular hypertrophy, and pregnancy.

Oral informed consent was obtained by the interventional cardiologist immediately after successful PPCI. A more extensive written informed consent was obtained after the procedure, either in the catheterization laboratory or in the coronary care unit. Twenty patients were permitted to be included by the institutional review board of the Catharina Hospital Eindhoven.

2.2. PPCI Procedure

Patients received aspirin (300 mg) and a loading dose of clopidogrel, ticagrelor or prasugrel in the ambulance according to routine. Before angiography, all patients received heparin (5000 IU). Primary PCI was performed according to standard clinical practice. Use of thrombosuction or adjunctive pharmacology such as glycoprotein IIb/IIIa receptor inhibitors was left to the discretion of the operator. When, immediately following successful PPCI, the patient met the inclusion criteria and had given informed consent, measurements of distal coronary pressure

and absolute coronary blood flow and resistance were performed as described below.

2.3. Invasive hemodynamic measurements

After successful PPCI of the culprit vessel, the guide wire was exchanged for one with distal pressure and temperature sensors (St Jude Medical, Minneapolis), whereafter distal coronary pressure, the index of microvascular resistance (IMR) and absolute flow were measured in the infarct-related artery as previously described in stable patients [9,10,12]. Maximal hyperemia, and thereby minimal microvascular resistance, was induced by using $140 \mu\text{g/kg/min}$ of intravenous adenosine via a central venous catheter. Absolute minimal resistance was calculated by dividing distal pressure by the absolute flow and expressed in $\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ per gram of tissue in the area at risk.

For determination of IMR, small bolus injections of 3 cm^3 of saline were given into the infarct-related artery as described by Fearon et al. [12]. This was done three times at hyperemia. Mean transit time (T_{mn}) and P_d were measured simultaneously. IMR was calculated by multiplying the mean P_d by the hyperaemic T_{mn} . IMR was taken as the average of the three consecutive measurements at hyperemia as described before [12].

2.4. Measurement of absolute coronary blood flow

Thereafter, absolute flow was measured. A small specially designed infusion catheter with four side holes in its most distal part was advanced over the pressure guide wire through the Y-connector. The tip of the infusion catheter was placed in the stent, i.e. at the level of the previous occlusion, and the sensor was placed in the distal part of the infarct related artery. The infusion catheter was then connected to an infusion pump by a second Y connector, enabling continuous infusion of saline at a rate of 20–30 ml/min (Fig. 1). The sensor-tipped guide wire was connected to the interface (Analyzer, St Jude Medical), and distal coronary pressure (P_d) and temperature were displayed simultaneously. The exact infusion rate was chosen depending on the size of the artery and at the discretion of the operator. Next, a continuous recording was made of P_d and distal blood temperature after complete mixing during constant saline infusion (Fig. 2). After a steady state had been achieved, the pressure/temperature sensor was pulled back into the infusion catheter so that the temperature of the saline (T_i) at the location of the most proximal side hole could be measured (Fig. 2). Using the technology of continuous infusion of saline at a low rate, absolute hyperaemic blood flow (Q_b) can be calculated by the infusion rate of saline (Q_i), temperature of the infused saline (T_i) and distal blood temperature after complete mixing (T), using the following equation:

$$Q_b = 1.08 \left[\frac{T_i}{T} - 1 \right] Q_i + Q_i \approx 1.08 \left[\frac{T_i}{T} \right] Q_i$$

The factor 1.08 corrects for the differences in specific heat between blood and saline. The protocol of absolute flow measurement was performed again at hyperemia after an interval of 5 min. The exact position of the sensor-tipped wire during measurements was documented on cine-angiography to make sure that the same position was chosen at the second exam 5 days later. All data were analyzed off line. Blood flow was expressed as ml/min and by adding the area at risk from CMR, blood flow per gram of tissue was calculated in ml/min/g for the area at risk.

After three to five days, control angiography of the infarct-related artery was performed followed by measurements of FFR, IMR and absolute flow using exactly the same position of the wire and infusion catheter as in the first procedure.

Fig. 1. Set-up for measuring absolute coronary blood flow during catheterization using the technology of continuous saline infusion at a low rate. A guide wire with distal pressure and temperature sensors is positioned in the distal part of the coronary artery. Next, a special infusion catheter with four small side holes in the last 5 mm proximal to its tip is advanced over the guide wire. This catheter is designed to ensure adequate mixing of blood and saline and has to be placed in the coronary artery. The infusion catheter is connected to an infusion pump. The distance between the distal tip of the infusion catheter and the position of the pressure/temperature sensor must be 3–6 cm. The sensor-equipped guide wire can then be connected to the interface for recording pressure and temperature (Analyzer; St Jude Medical Systems). Absolute hyperaemic coronary blood flow (Q_b) can be calculated by the infusion rate (Q_i), temperature of the infused saline (T_i) and distal blood temperature after complete mixing (T). (See equation in text).

2.5. Cardiovascular magnetic resonance (CMR)

CMR was performed 3–5 days after the index procedure, preferably on the same day as the second invasive procedure. CMR was performed on either of two 1.5 T systems: Siemens or Magnetom Vision. Cine images were acquired on a 1.5 T scanner (Ingenia CV, Release 4.1.3.0 Philips Medical Systems, Best, The Netherlands) with electrocardiographic gating.

All subjects were placed in a supine position and short-axis, four-chamber, two-chamber and 3-chamber views were acquired during an end expiratory breath hold. Left ventricular function was assessed by a standard steady-state free precession technique (repetition time 3.3 ms, echo time 70 ms, flip angle 60 degrees, slice thickness 8 mm, slice gap 0 mm). An example of a mid LV short-axis image is shown in Fig. 3.

For determination of the area at risk, we obtained short-axis slices covering the whole ventricle using a T2-weighted triple inversion recovery breath-hold pulse sequence (repetition time 2000 ms, echo time 70 ms, flip angle 90 degrees, slice thickness 8 mm, slice gap 0 mm).

All CMR images were analyzed using the freely available software Segment v 1.8 <http://segment.heiberg.se> (Heiberg et al. BMC med imaging 10: 1, 2010).

The left ventricular (LV) mass was assessed on the cine images by manual tracing of the endocardial and epicardial borders with exclusion of the papillary muscles.

The AR was derived from the T2-weighted imaging and defined as the total amount of hyperintense myocardium in all short-axis slices and expressed as a percentage of LV mass. All endocardial and epicardial tracings were performed by two observers blinded to the clinical data. They had to agree and provide the final percentage of the area at risk. Offline recalculation was done to obtain the AR and LV mass in grams.

2.6. Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD), or median and interquartile range (IQR), as appropriate. Flow was expressed as ml/min/g. Resistance was expressed as dyne.sec.cm-5/g. IMR was expressed as dimensionless index (arbitrary units). Due to the maximal vasodilated state of the coronary circulation, a linear relationship was assumed to exist between perfusion pressure and blood flow [13]. To compare the multiple measurements of flow over time within the same patient at different perfusion pressures, pressures were normalized to the initial aortic pressure (P_a) as proposed by Fearon et al. [8]. IMR values at the initial measurement in the hyperacute phase of STEMI were divided in two groups, high and low, separated by the median value.

For evaluation of absolute flow and resistance over time within the same patient, each patient was his own control after normalization for aortic pressure. For comparison of flow and resistance between different patients, AR by CMR was used to calculate flow in ml/min/g of tissue,

Fig. 2. Example of absolute flow measurement by continuous thermodilution and saline infusion in a STEMI patient. On the left, blood temperature at steady state hyperaemia (T_b) is set to zero (corresponding to normal blood temperature). Next, saline infusion is started (arrow) at the location of the previous occlusion (stent) and temperature T in the distal coronary artery after complete mixing is recorded during steady state infusion. Finally, the sensor is pulled back into the tip of the infusion catheter (asterisk) to measure the temperature of the infused saline (T_i). Absolute flow is then easily calculated according to the equation. These measurements can be continued for an arbitrary time and are completely operator independent. Notice that aortic pressure (P_a) via the guiding catheter and distal coronary pressure (P_d) via the guide wire's pressure sensor are also measured. Notice also that withdrawal of the pressure sensor into the infusion catheter is marked by the sudden increase of the pressure signal.

by dividing absolute flow and resistance by the mass of the AR. Differences between groups were assessed by the paired t-test for continuous data with a normal distribution. Otherwise, the nonparametric Wilcoxon rank-sum test was used.

3. Results

Twenty patients enrolled in the study. Five patients withdrew informed consent after the first procedure. Consequently, flow and resistance data were available for 20 patients in the acute phase of STEMI

and in 15 patients after 3–5 days. CMR was available in 16 patients. In one patient all invasive measurements were performed successfully, but it was not possible to analyze the CMR images accurately because of low image quality and, therefore, flow could not be related to the AR in that patient.

Baseline clinical and angiographic characteristics are presented in Table 1. The left anterior descending artery was the culprit vessel in 8 cases, the right coronary artery in 8 cases, and the left circumflex artery in 4 cases. In 8 patients, the culprit vessel was not totally occluded at presentation. After PPCI, TIMI 3 flow was achieved in all cases.

Fig. 3. Corresponding mid-ventricular short-axis slices in a single patient with an occlusion of the left anterior descending coronary artery. The endocardium is traced in red and the epicardium is traced in green. Left: The myocardium at risk is traced in white on the T2-weighted CMR image. Right: The infarcted region is traced in yellow/pink on the late gadolinium enhanced (LGE) CMR image. Within the infarct a hypointense region (dashed red line) can be seen without the presence of gadolinium, representing an area of no-reflow or microvascular obstruction.

Table 1

Clinical and angiographic characteristics at baseline.

Variable	n	=	20
Age, yrs	57	±	9
Male	16		(80%)
Risk factors			
Diabetes	2		(10%)
Hypertension	3		(15%)
Hyperlipidemia	4		(20%)
Family history of CAD/PAD	9		(45%)
Smoking	14		(70%)
Onset symptoms -reperfusion (min)	162		
Localization culprit lesion			
LAD	8		(40%)
RCA	8		(40%)
CX	4		(20%)
Reference diameter culprit vessel (mm)	3.4	±	0.4

Measurements of invasive and CMR indices are shown in Table 2. Measuring FFR in the acute phase does not make any sense, but FFR in the subacute phase showed that epicardial revascularization had been successful in all patients. A saline infusion rate of 20 ml/min was used except in patients number 17 and 18, in whom 30 and 25 ml/min was used, respectively, because of the large diameter of the culprit artery. All measurements related to this protocol were completed within 25 min. In one patient in whom the RCA was the culprit artery, brief, transient second-degree AV block occurred without hemodynamic consequence. No other complication occurred due to the invasive measurements either in the hyperacute phase or in the subacute phase. Fig. 4 shows the changes in absolute coronary blood flow in the AR over time. In healthy individuals, maximum absolute blood flow equals 3.7–6.5 ml/min/g [14]. In our study, average hyperaemic blood flow to the AR was 3.14 ± 1.64 ml/min/g in the hyperacute phase and 3.68 ± 1.93 ml/min/g after 3–5 days ($p = 0.25$). Some patients showed a remarkable increase in coronary blood flow over time, whereas in others coronary blood flow did not change or even became slightly lower.

Absolute resistance in the hyperacute phase could be calculated for all patients and varied from 21,789 to 160,000 dyne.sec.cm-5. Average absolute resistance in the AR decreased from 1317 dyne.sec.cm-5/g in the hyperacute phase to 1099 dyne.sec.cm-5/g after 3–5 days ($p = 0.40$; Fig. 4). A high IMR directly after PPCI was associated with a lower absolute flow to the area at risk, whereas low IMR was associated with an almost normal myocardial flow ($p = 0.15$; Fig. 5).

4. Discussion

This study performed the first absolute coronary flow measurements in acute STEMI patients using the technique of thermodilution with continuous infusion of saline. Repeat measurements in the same coronary artery were performed after a time interval of several days. We showed that measurement of absolute coronary blood flow is safe and feasible in STEMI patients.

The interpretation of absolute flow in the infarcted area is not trivial. First, the measured value should be related to the AR, for which a cardiac magnetic resonance imaging exam within a few days is mandatory. Second, absence of change between the hyperacute and subacute phase can indicate either minimal initial damage as a result of effective and timely PPCI, or extensive damage without recovery. By relating flow to mass, those two different states can be distinguished. An increase in absolute maximum flow between the hyperacute and subacute phase most likely indicates recovery, as it reflects the decrease of minimal microvascular resistance in the AR.

Currently the invasive index typically used to characterize qualitative microvascular (dys)function in STEMI is the index of microvascular resistance (IMR). In our study, a clear correlation was found between IMR and absolute flow in the hyperacute phase (Fig. 5).

The median IMR of 22 in our study is lower than in the study by Fearon et al., where the median IMR was 32 [8]. This difference could be explained by a shorter “onset-of-pain to balloon time” in our study (mean 287 ± 138 versus 162 ± 122 min).

IMR measurement in STEMI patients offers the opportunity to identify inadequate myocardial reperfusion after PPCI, but is limited by its operator dependency and relatively high variability. Because the technique of measuring absolute blood flow as in this study allows repeated measurements over time with little variation and is fully operator independent, we expect that absolute flow measurement in the infarct related artery is a potentially more reliable tool to evaluate the effect of therapy over time within one individual patient. Nevertheless, interpretation of absolute coronary flow as a single value still remains difficult due to large interindividual variability related to the AR. A relatively high flow could be normal in one patient if the dependent perfusion territory is small, but low for another patient with a large perfusion territory. For these reasons, in contrast to IMR, estimation of myocardial mass by CMR is necessary to interpret absolute flow in a useful way. In addition, a potential limitation of this methodology could be the volume load associated with these measurements. In our study, however, infused volume was rather modest (flow rate ≤ 30 ml/min and total infusion 200 ml in all patients) and not expected to give clinical problems. Lack of measurement in a control artery is not a real limitation because the IRA serves as its own control. Finally, although this technique is not difficult, instrumentation is not trivial and a special infusion catheter and software (St Jude Medical) is necessary. For these reasons this technique will be limited to research purposes for the present time, in contrast to IMR.

4.1. Study limitations

This was a small study in only 20 selected patients, and larger data series are needed to explore further the therapeutic consequences of measuring absolute coronary blood flow. Potential future studies could use it to identify high-risk patients, monitor the effect of drugs administered during PPCI such as glycoprotein IIB/IIIA-inhibitors or nitroglycerine, or better evaluate the effect of an intra-aortic balloon pump.

5. Conclusion

The technique of thermodilution using a modest, continuous, intracoronary infusion of saline permits safe and feasible measurement of absolute coronary blood flow and microvascular resistance during PPCI in STEMI patients. This technique may allow better exploration and understanding of microvascular (dys)function in the early phase of STEMI. Absolute blood flow per gram of tissue of myocardium at risk correlates well with IMR. During the first couple of days absolute flow increases and resistance decreases in a considerable number of patients, indicating recovery of microvascular dysfunction over time. Larger studies are mandatory to evaluate the clinical consequences of these kinds of measurements.

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Disclosures

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Table 2
Hemodynamic and CMR measurements.

No	TIMlpre	AR (g)	LVmass (g)	AR/LV mass (%)	IMR0	IMRFU	Q0 (ml/min)	QFU (ml/min)	QAR,0 (ml/min/g)	QAR,FU (ml/min/g)	Δ QAR (%)	R0 (dyne.sec.cm-5)	RFU (dyne.sec.cm-5)	R0,AR (dyne.sec.cm-5)/g	RFU,AR (dyne.sec.cm-5)/g	FFRFU	R _{FU,AR} (dyne.sec.cm ⁻⁵)/g	FFR _{FU}
1	0	33	121	27%	60	14	34	173	1,05	5,29	407%	160,000	34,444	4893	1053	0,95	1053	0,95
2	0	33	102	32%	15	37	120	106	3,68	3,26	–11%	37,377	39,273	1147	1205	0,98	1205	0,98
3	2	—	—	—	18	31	225	186	—	—	—	26,544	22,919	—	—	0,88	—	0,88
4	0	45	142	32%	33	27	171	232	3,76	5,11	36%	32,093	27,208	707	599	0,98	599	0,98
5	0	22	110	20%	52	14	96	143	4,38	6,52	49%	55,758	40,795	2534	1854	0,85	1854	0,85
6	0	—	—	—	31	—	143	—	—	—	—	43,590	—	—	—	—	—	—
7	0	52	106	49%	11	18	44	111	0,85	2,13	151%	127,347	53,543	2454	1032	0,95	1032	0,95
8	3	54	198	27%	16	12	174	171	3,26	3,19	–2%	28,571	31,678	534	592	0,96	592	0,96
9	0	56	140	40%	68	10	86	80	1,53	1,44	–6%	48,352	49,032	863	876	0,96	876	0,96
10	0	31	140	22%	11	16	168	148	5,45	4,81	–12%	23,902	30,330	776	985	0,9	985	0,9
11	0	26	145	18%	22	14	157	182	6,03	6,99	16%	33,121	30,870	1269	1183	0,97	1183	0,97
12	3	—	—	—	9	—	102	—	—	—	—	48,762	—	—	—	—	—	—
13	2	48	101	47%	16	21	149	158	3,13	3,33	6%	48,312	35,789	1017	753	0,82	753	0,82
14	3	101	151	67%	23	13	199	96	1,96	0,95	–52%	31,414	59,592	310	589	0,83	589	0,83
15	0	27	156	17%	15	32	98	46	3,70	1,73	–53%	39,588	100,984	1494	3811	0,99	3811	0,99
16	0	50	135	37%	50	—	118	—	2,35	—	—	31,736	—	635	—	—	—	—
17	1	97	220	44%	65	61	103	194	1,07	2,00	88%	54,154	28,980	559	299	0,86	299	0,86
18	2	53	157	34%	20	21	258	255	4,83	4,78	–1%	29,921	29,395	560	550	0,91	550	0,91
19	2	—	—	—	36	—	251	—	—	—	—	21,789	—	—	—	—	—	—
20	0	—	—	—	85	—	76	—	—	—	—	53,684	—	—	—	—	—	—

0 indicates time of infarction.

FU indicates 3–5 days after infarction (follow-up).

FFR = fractional flow reserve.

IMR = index of microvascular resistance.

AR = area at risk.

LV mass = left ventricular mass.

Q = absolute coronary blood flow (ml/min).

QAR = absolute coronary blood flow corrected for area at risk (ml/min/g).

R = absolute minimal resistance (dyne.sec.cm-5).

RAR = absolute minimal resistance corrected for area at risk (dyne.sec.cm-5)/g.

Fig. 4. Absolute coronary blood flow to the area at risk at the time of infarction immediately after PPCI (t_0), and 3–5 days post-infarction (t_5). The shadowed area indicates the range of normal maximum myocardial blood flow in healthy persons (upper panel). The lower panel shows the absolute minimal resistance at the time of infarction and after 3–5 days.

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Fig. 5. Box and whisker plots for absolute flow corrected for the area at risk (AR) according to high and low index of microvascular resistance (IMR). The box limits represent the 10th and 90th percentiles. The horizontal line within the box represents the median value.

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