Biomarkers of Coronary Endothelial health: correlation with invasive measures of collateral function, Flow and Resistance in Chronically Occluded Coronary Arteries and the Effect of Recanalization

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Abstract

Objectives

In the presence of a chronically occluded coronary artery, the collateral circulation matures by a process of arteriogenesis, however there is considerable variation between individuals as to the functional capacity of that collateral network. This could be explained by differences in endothelial health and function. We endeavoured to examine the relationship between functional extent of collateralisation and levels of biomarkers which have been shown to relate to endothelial health.

Methods

We measured four potential biomarkers of endothelial health in 34 patients with mature collateral networks who underwent successful percutaneous coronary intervention (PCI) to a chronic total coronary occlusion (CTO) prior to PCI and 6-8 weeks post-PCI and examined the relationship of biomarker levels with physiological measures of collateralisation.

Results

We did not demonstrate a significant change in systemic levels of sICAM-1, sE-selectin, microparticles or tissue factor 6-8 weeks after PCI. We did demonstrate an association between estimated retrograde collateral flow prior to CTO recanalization and lower levels of sICAM-1 (r=0.39,p=0.026), sE-selectin (r=0.48, p=0.005) and microparticles (r=0.38, p=0.03).

Conclusions

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Recanalization of a CTO and resultant regression of a mature collateral circulation does not alter systemic levels of sICAM-1, sE-selectin, microparticles or tissue factor. The identified relationship of retrograde collateral flow with sICAM-1, sE-selectin and microparticles is likely to represent an association with an ability to develop collaterals rather than their presence and extent.

Condensed abstract

The functional capacity of collateral networks between patients with CTOs varies considerably. This could be explained by differences in endothelial health and function. Four potential biomarkers of endothelial health were measured in 34 patients with mature collateral networks who underwent successful PCI to a CTO prior and the relationship between biomarker levels with physiological measures of collateralisation was examined. We found no significant change in systemic levels of sICAM-1, sE-selectin, microparticles or tissue factor when baseline measures were compared with those at follow-up. We did find an association between estimated retrograde collateral flow prior to CTO recanalization and lower levels of sICAM-1, sE-selectin and microparticles. Regression of a mature collateral circulation does not alter systemic levels of sICAM-1, sE-selectin, microparticles or tissue factor. Any relationship of retrograde collateral flow with sICAM-1, sE-selectin and microparticles is likely to represent an association with an ability to develop collaterals rather than their presence and extent.

Introduction

In response to a chronically occluded coronary artery, coronary collaterals develop which supply the myocardium distal to the occlusion and are often sufficient to preserve resting left ventricular systolic function in spite complete coronary occlusion[1,2]. Our current understanding is that growth of a network of pre-existing anastamotic arterioles, termed arteriogenesis, occurs independently of an ischaemic stimulus by means of mechanical transduction of endothelial shear stress, stimulating a cascade of growth factors and inflammatory mediators[3]. However there is considerable variability to the extent of functional collateral supply that individuals develop[4]. A number of studies have suggested associations between biomarkers thought be involved in the arteriogenic process and functional collateralisation[5–10]. However the significance of any difference in biomarkers levels between individuals with 'good' and 'poor' functional collateralisation is not clear. Any identified associations may reflect a direct relationship between extent of collateralisation and the biomarker in question, a relationship between biomarker levels and endothelial or circulatory health, or a relationship with active arteriogenic activity (which could mean biological factors active in the process could be higher in individuals with less well developed or less well matured collateral circulations).

Both ICAM-1 and E-selectin have been implicated in the arteriogenic process[5,11,12]. Microparticles are thought to play an important role in endothelial function, and may relate to endothelial health[13], and tissue factor has been shown in vitro to be involved in the

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regulation of both endothelial[14] and smooth muscle cell[15] proliferation, both of which are thought to be integral to the arteriogenic process.

We endeavoured to investigate the relationship of these four potential biomarkers with indices of collateral flow, resistance and functional collateralisation in a population undergoing successful PCI to a CTO, all with well established collateral networks. Serum biomarkers were measured at the time of the procedure and at follow-up to investigate the effect of the presence of an active collateral network on biomarker levels.

Methods

Study patients

Thirty four patients who underwent successful PCI to a CTO for symptoms of angina (Canadian Cardiovascular Society (CCS) class 1-3) were recruited consecutively in a single tertiary centre between January 2013 and June 2014. A CTO was defined as complete coronary occlusion of ≥3 months duration with TIMI grade 0 flow[16]. Exclusion criteria were inability to provide consent, >1 occluded vessel, prior CABG with any patent grafts, left main stem stenosis considered to be haemodynamically significant and contra-indications to adenosine. All included patients had right dominant coronary anatomy. The presence of viable myocardium in the CTO territory was confirmed in all patients by myocardial perfusion scintigraphy(n=26, 76.5%), dobutamine stress echocardiography(n=1, 2.9%) or by the absence of a wall motion abnormality by echocardiography or left ventricular angiography without additional confirmation(n=7, 20.6%). Patient's usual medications were continued and they were asked to abstain from caffeine for 48 hours prior to the procedure.

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Ethics

The study protocol was approved by the local research ethics committee (12/YH/0360). All subjects provided written informed consent.

Catheter laboratory protocol

Dual arterial access was used for all procedures. Femoral venous access was obtained for central administration of adenosine and measurement of central venous pressure(CVP) at the beginning and end of the procedure using a catheter positioned in the right atrium.

Before PCI, and at the end of the procedure, 20ml of blood was aspirated from the catheter in the right atrium. At the same time as the pre-PCI right atrial sampling, 20ml of blood was aspirated from the femoral arterial sheath. At follow-up, 6-8 weeks after the successful procedure, 20ml of blood was sampled from a peripheral vein.

After initial blood sampling, patients were anti-coagulated with 100 U/kg of unfractionated heparin to maintain an activated clotting time of >300 seconds. A 200mcg bolus of intra-coronary glyceryl trinitrate(GTN) was given and iso-centred coronary angiograms of both non-target vessels were taken.

The haemodynamic assessment protocol has been described previously[17]. Briefly, a dual sensor pressure-velocity 0.014" intracoronary wire (Combowire, Volcano Corp, San Diego, CA)[18] was connected to a ComboMap console (Volcano Corp) and used for

haemodymamic measurements. In order to estimate absolute coronary flow in the non-target vessels, the wire was advanced to the segment of the non-target vessel proximal to any major side-branches and manipulated to obtain a good Doppler trace. After administration of 100mcg intra-coronary GTN, once the hyperaemic response had settled, continuous recordings from the ComboMap were taken. Samples were recorded at 200Hz and stored on disk for offline analysis.

PCI of the CTO was undertaken at the discretion of the treating interventional cardiologist using an antegrade or retrograde approach. Once access to the vessel lumen distal to the point of occlusion was achieved, prior to restoration of antegrade flow, a microcatheter was placed into the distal vessel to facilitate delivery of the Combowire. The wire was normalised to aortic pressure at the tip of the catheter, alongside the microcatheter, removed and advanced through the microcatheter to the distal segment of each non-target vessel and manipulated to obtain a good Doppler trace. After administration of 100mcg intra-coronary GTN, once the hyperaemic response had settled, continuous recordings from the ComboMap were taken. Hyperaemia was achieved by central venous administration of adenosine at 140 mcg/kg/minute. Once steady state hyperaemia had been reached and a continuous recording of $\geq$20 beats taken, adenosine infusion was ceased. Samples were recorded at 200Hz and stored on disk for offline analysis.

PCI success was defined as stenting of the target vessel with <30% residual stenosis and thrombolysis in myocardial infarction (TIMI) grade III flow. After successful PCI, non-target and target vessel haemodynamic measurements were repeated as described pre-procedure, at the site of the previous measurement.

Recorded data was analysed using dedicated custom software (Study Manager, Academic Medical Center, University of Amsterdam, The Netherlands)

Angiographic assessment

Proximal non-target vessel diameters (at the point of proximal haemodynamic measurement) measured in two orthogonal views were calculated by two independent observers using quantitative coronary angiography(QCA)(GE Centricity CA1000, GE Healthcare) using the guiding catheter luminal diameter as reference. Mean values from both observers were used for analysis. The vessel collateral connection(CC) grade[19] and modified Rentrop score[20] were assessed by two independent observers blinded to haemodynamic measurements and agreed by consensus.

Data analysis

Fractional collateral flow reserve was calculated as (Pd-CVP)/Pa-CVP), using mean pressures taken over 5 cardiac cycles at stable hyperaemia[21], with Pd measured in the occluded segment of the artery, prior to restoration of antegrade flow[22]. Collateral flow velocity reserve was calculated with flow velocities in the occluded segment measured at rest and steady state hyperaemia[23] as APV at steady state hyperaemia divided by APV at baseline, measured over 5 cardiac cycles. The resistance index of the collateral supply pathway, incorporating both the resistance of the collateral vessel and of the donor segment proximal to the collateral take-off was calculated as: $R_{Coll} = (P_{Ao} - P_d)/APV_d$ ($mmHg \cdot cm^{-1} \cdot s^{-1}$)[6,24]. The peripheral resistance index, or the resistance in the target (collateral recipient) vessel downstream of the collateral supply was calculated as: $R_P = P_d/APV_d$ ($mmHg \cdot cm^{-1} \cdot s^{-1}$)[6,24].

The difference in combined non-target vessel absolute flow before and after successful CTO PCI should approximate to absolute flow through the retrograde collateral network (although would not include the contribution of antegrade bridging collaterals).For the purposes of estimating non-target vessel flow, absolute coronary flow was estimated as

(πx proximal vessel radius^2)x(proximal vessel APV/2)[25,26]. As resting absolute myocardial blood flow is closely related to rate pressure product(RPP), values for resting absolute coronary flow were divided by the respective RPP/10,000[27].

Biomarker assays

For the measurement of sICAM-1 and sE-selectin, blood samples were drawn into serum separator tubes, allowed to clot for 30 minutes prior to centrifugation and centrifuged for 15 min at 1000g. The separated serum was stored in aliquots at −80°C to permit assay in batches. The concentration of sE-Selectin and sICAM-1 were determined using a commercially available specific sandwich enzyme-linked immunosorbent assay (ELISA) kit (Quantikine, R&D Systems). Briefly, ELISA plates pre-coated with a specific capture antibody were used, standards and samples were added to the plate and incubated for 2 hours at room temperature. The bound soluble adhesion molecule of interest was detected by a further 2 hour incubation with a specific antibody conjugated to horseradish peroxidise followed by a 30 minute incubation with stabilized hydrogen peroxide and tetramethylbenzidine. The reaction was stopped by the addition of 2 N sulphuric acid to each well and the optical density at 450nm measured using a microplate reader (BMG Labtech, Aylesbury, United Kingdom).

For the measurement of plasma microparticles blood samples were drawn into vacutainer tubes containing 0·11 mol/l sodium citrate, centrifuged for 15 minutes at 1,500g at room temperature. Plasma supernatant was then rapidly centrifuged for 2 minutes at 13,000g. The separated 'platelet free' plasma was stored in aliquots at −80°C to permit assay in batches. Microparticles concentrations were determined using a commercially available specific ELISA kit (ZYMUPHEN MP-Activity, Hyphen BioMed, Quadratech, Epsom,

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United Kingdom). Briefly, the diluted plasma sample or standard, supplemented with calcium, Factor Xa and thrombin inhibitors was added to a microplate pre-coated with Streptavidine and biotinylated Annexin V and incubated at 37°C for 1 hour. After a washing step, a Bovine factor Xa-Va mixture containing calcium and purified human Prothombin are added to each well and incubated for a further 10 minutes at 37°C. Thrombin specific chromogenic substrate was then added to each well, after 3 minutes 2% Citric acid was added as a stop solution to each well and optical density at 405nm measured using a microplate reader (BMG Labtech).

For the measurement of plasma TF levels, blood samples were drawn into vacutainer tubes containing 0·11 mol/l sodium citrate, centrifuged for 15 minutes at 3,000g and stored in aliquots at −80°C to permit assay in batches. TF was measured by ELISA. Briefly, microtitre ELISA plates were coated overnight with a specific TF capture antibody (sheep anti-Human Tissue Factor, Enzyme Research Laboratories, Swansea, United Kingdom) in 50 mmol carbonate buffer pH = 9.6. The plates were then incubated overnight at 4°C with PBS/Bovine serum albumen blocking buffer. After a washing step, standards (diluted recombinant tissue factor, American Diagnostica inc, Stanford, USA) and samples were added to the plate and incubated for 90 minutes at room temperature. After another washing step, anti-TF IgG conjugated to horseradish peroxidise was added to the plates and incubated for 90 minutes at room temperature. The plates were washed again and a tetramethylbenzidine substarte solution added and agitated at room temperature for 15 minutes. The reaction was stopped by the addition of 2 M sulphuric acid to each well and the optical density at 490nm measured using a microplate reader (BMG Labtech).

The intra-assay coefficient of variation of the ELISA measurements was 9.2% for sICAM-1, 9.3% for sE-Selectin, 9.5% for microparticles and 13.8% for TF. Inter-assay

coefficients were 7.1% for sICAM-1, 12.9% for sE-Selectin, 11.6% for microparticles and 14.7% for TF.

Biomarker comparsions and correlations

To establish if biomarkers levels in the right atrium were elevated relative to sample sites remote from the heart, right atrial biomarker levels were compared with levels taken from the femoral arterial sheath prior to PCI. To investigate if there had been a change in biomarker levels between prior to PCI and follow-up, right atrial biomarker levels taken prior to PCI were compared with those from a peripheral venous sample taken at follow-up. Correlations were tested between right atrial biomarker levels and FFRcoll, CollFVR, the change in non-target baseline flow after PCI (Δcombined non-target vessel baseline flow, an approximation of retrograde collateral flow after PCI), R_{Coll} and R_P.

Statistical analysis

Stata v.12(StataCorp) was used for statistical analysis. Continuous values are expressed as means±SD, or median(25th percentile-75th percentile) as appropriate. Continuous variables were compared using a paired t-test or Wilcoxon signed-rank test. Correlations were quantified using Pearson's correlation coefficient. Probability values were 2-sided, and values of p<.05 considered significant.

Results

Pre-procedural biomarker levels were taken in all 34 successful cases, follow-up levels were taken at between 6 and 8 weeks post PCI in 30. Drug-eluting stents were used for all procedures. Demographics, angiographic and procedural details are shown in **Table 1**.

Haemodynamic measures of functional collateralisation

Table 2 lists summary statistics for measures of functional collateralisation, collateral flow and resistance. Measures of collateral perfusion are only included if the vessel distal to the occlusion was accessed antegradely (n=28). As one of those patients had inadequate flow traces, combined pressure and flow measurements taken distal to the occlusion are only included in 27 patients. Pre and post PCI donor vessel flow measurements were possible in 32 of 34 patients. Mean combined absolute baseline flow in both non-target vessels, adjusted for rate pressure product reduced from 335.0 ml· min^{-1} prior to PCI to 281.3 ml· min^{-1} post-PCI (difference -53.8 ml· min^{-1}, 95% CI -93.9 to -13.6, p=.01). Mean combined absolute hyperaemic flow in both non-target vessels reduced from 580.8 ml· min^{-1} prior to PCI to 543.6 ml· min^{-1} post-PCI (difference -37.2 ml· min^{-1}, 95% CI -75.5 to 0.1, p=0.056).

Biomarker levels

Levels of all four measured biomarker levels are depicted in figure 1. We found no veno-arterial gradient in levels of any of the biomarkers. Biomarker levels taken at follow up from a peripheral vein were also not significantly different from arterial samples taken immediately prior to PCI when the collateral pathway was still 'active'.

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Figure 2 shows the relationship between pre-procedural right atrial biomarker levels and measures of collateral perfusion. Although we did not demonstrate a relationship between any of the biomarkers and measures of collateralisation taken distal to the point of occlusion prior to recanalization, we did demonstrate a significant correlation between the change in baseline non-target vessel flow and levels of sICAM-1, sE-selectin and microparticles. We found no correlation between any biomarker and measures of collateral pathway resistance R_{coll} (sICAM-1 r=0.10, p=0.57; sEselectin r=0.14, p=0.46; microparticles r=0.16, p=0.39; TF r=-0.06, p=0.75) or the resistance of the collateral recipient vessel downstream of the collateral supply R_P (sICAM-1 r=0.09, p=0.65; sEselectin r=-0.18, p=0.33; microparticles r=0.09, p=0.64; TF r=-0.15, p=0.44).

Discussion

In a population with established extensive collateral networks, with a median duration of coronary occlusion in excess of 1 year, we demonstrate no significant reduction in systemic sICAM-1, sE-selectin, microparticle or TF levels at 6-8 weeks after CTO recanalization. We have also not demonstrated a gradient in levels of these biomarkers between the right atrial and femoral arterial circulation when the collateral network was still present and 'active'. In addition, we have found no association between established guidewire based indices of collateral perfusion (FFRcoll and CollFVR) and biomarker levels. We have however demonstrated an association between change in summed non-target CTO vessel flow and levels of sICAM-1, sE-selectin and microparticles, which is likely to represent an association between retrograde collateral absolute flow prior to CTO recanalization and each biomarker.

The absence of a veno-arterial gradient

We found no significant difference in any biomarker levels if they were sampled in the right atrium compared with samples taken remote from the heart through the femoral arterial sheath. This suggests peripherally taken samples at follow up are representative of levels in the right atrium. A limitation of the current study is that we did not take samples from the coronary sinus, or beyond the occluded segment. It is possible that levels of biomarkers taken in this way may have been higher than in the systemic circulation.

No reduction in biomarker levels at follow-up

In previous studies which have demonstrated relationships between collateral perfusion (whether functional or angiographic) and biomarker levels[5–10], including some of the biomarkers measured here[5], a more heterogeneous patient population was included than in this study. In those studies which included patients with non-occlusive disease, lesions of differing physiological severity must have been included[5,7–10]. A difference in basic fibroblast growth factor has been identified in coronary occlusions of <3 months duration compared with those of ≥3 months in duration (what we would now consider to be a CTO[16]). It is conceivable that other growth factors implicated in the arteriogenic process might show a similar relationship with duration of occlusion. The population included in this study all had a well developed collateral circulation with Rentrop grade 2-3 and CC grade 1-2 angiographic collateralisation in all patients and coronary occlusion which had been present for at least 3 months (median 53 weeks). If biomarker levels related directly to extent of collateralisation, then one would expect that after the chronically occluded vessel is

recanalized, that biomarker levels would fall. This was not the case in any of the four biomarkers that we measured.

Extent of collateralisation does not necessarily reflect level of arteriogenic activity. In fact, a less well developed collateral circulation may reflect more recent coronary occlusion or progression of flow limitation caused by a coronary stenosis. The various differences in biochemical activity that have been reported between individuals of differing degrees of collateralisation may reflect an active arteriogenic process in the less well collateralised patients. Our results, showing no difference in biomarker levels 6-8 weeks after recanalization in a population with well established collaterals would be in keeping with, but are not necessarily supportive of that hypothesis.

In ICAM-1 and sE-selectin we chose to investigate two biomarkers which appear to have a clear role in arteriogenesis[3,12]. Both are involved in the adhesion of macrophages to shear-stress activated collateral endothelium, an important step in the arteriogenic process and ICAM-1 expression has been shown to be stimulated by increased shear stress[11]. In animal models, arteriogenesis is reduced in the presence of ICAM-1 deficiency[12]. Both sICAM-1 and sE-selectin have been shown to be at higher levels in patients with a lower angiographic grade of collateral[5]. Our finding that their level did not decrease after CTO recanalization would suggest that any relationship between extent of collateralisation does not relate to the presence of an established collateral circulation, but more likely the ability to form one.

Biomarker levels: relationship with collateral flow

We were unable to demonstrate a relationship between invasively derived measures of collateral perfusion and resistance and any of the four biomarkers we tested (figure 2).

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One might expect functional measures of collateralisation to be more reliable than angiographic measures and a relationship therefore easier to identify[19]. However, the number of patients in our study was small and even excluding measures in which the collateral dependent vessel was accessed via retrograde collaterals; antegrade access was gained by a dissection re-entry approach in a sizeable proportion of patients, which may have altered measures of collateral perfusion. Regardless of approach to CTO recanalization, collateral flow diminishes rapidly after restoration of antegrade flow[22,28]. The change in flow in the other major epicardial arteries should represent an approximation of retrograde collateral flow in the presence of a CTO. Given the limitations of multiple testing, the correlations that we have identified between change in donor vessel flow and levels of sICAM-1, sE-Selectin and microparticles can only be viewed as hypothesis generating. Nevertheless, the presence of a similar correlation between three of the four biomarkers that we have studied is interesting and is consistent with previous published findings[5].

Markers of endothelial health: a possible explanation

Arteriogenesis is a complex, endothelium dependent process and it is perhaps too much to expect a single biomarker to reflect arteriogenic activity or capacity. The levels of biomarkers that we have investigated have all been shown to be related to what could be considered to be endothelial health[14,29–33], lower levels of each being associated with a more 'healthy endothelium'. Angiographic extent of collateralisation has previously been shown to be associated with endothelial function in recanalized segments of CTOs[34]. This may well extend to an association between global coronary (and possibly systemic) endothelial health and the ability for collateral maturation. The various studies (including this one) which have demonstrated an association between various biomarkers levels and

extent of collateralisation, may be indirectly describing the same link between endothelial health and arteriogenic capacity.

Limitations

This is a single centre study, with a small number of patients. However, the population all had well developed collateral networks and we made comparison to biomarker levels both in the presence and absence of a collateral network supplying an occluded coronary segment and also to coronary haemodynamics associated with that change.

It is possible that biomarker levels taken from the coronary sinus or occluded coronary segment (through a microcatheter) may have been higher than in the right atrium or systemic circulation. However a number of studies have related systemic levels of biomarker to collateral development[5,8–10], so these measures remain pertinent. In addition, without systemic measures of biomarkers, it would not have been possible to take samples at follow-up for comparison.

An important limitation is that we tested for biomarker correlations with multiple physiological indices and these correlations should therefore be interpreted with caution. The significant correlations we have identified are related to one another however and have a plausible unifying biological explanation. Finally, our estimate of retrograde collateral flow ignores any antegrade bridging collaterals; this might have resulted in an underestimation of collateral flow in some patients.

Conclusions

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In patients with established collateral circulations supplying viable myocardium distal to CTOs, systemic levels of ICAM-1, sE-selectin, microparticles and TF do not reduce at follow up after recanalization of the CTO. Levels of ICAM-1, sE-selectin, microparticles are related to estimated total retrograde collateral flow prior to recanalization, which is most likely explained by an association with the ability to develop a collateral supply.

A possible biological explanation is that those with greater endothelial health have a greater capacity for arteriogenesis, however further studies would be required to examine this hypothesis further.

Tables

Table 1. Baseline Characteristics, Angiographic, and Procedural Details

|	
Demographics(n=34)	
Male, n(%)	27(79.4)
Age	60.8±9.6 y
Left ventricular ejection fraction(%)	56.2±11
Estimated occlusion duration(weeks)	53(30-104)
CCS class I/II/III/IV	8/20/6/0
Previous PCI, n(%)	9(26.5)
Previous myocardial infarction, n(%)	10(29.4)
Hypertension, n(%)	6(17.7)
Diabetes Mellitus, n(%)	5(14.7)
Current smoker, n(%)	10(29.4)
Angiographic details	
CTO vessel(RCA/LCx/LAD)	21/4/9
Rentrop collateral grade(1/2/3)	0/12/22
Maxiumum CC grade(0/1/2)	0/18/16
Procedural details	
Number of stents 1/2/3/4/5	6/11/10/6/1
Length of stent(mm)	74.5(44-101)
Means of recanalization	
Antegrade lumen-lumen, n(%)	19(55.9)
Antegrade dissection re-entry, n(%)	9(26.5)
Retrograde lumen-lumen, n(%)	3(8.8)
Retrograde dissection re-entry, n(%)	3(8.8)

Table 2. Haemodynamic measures of functional collateralisation

FFRcoll*	**0.38±0.12**
CollFVR†	**1.07±0.25**
R_{Coll}† (mmHg · cm^{-1} · s^{-1})	**4.87 (2.82-7.04)**
R_P† (mmHg · cm^{-1} · s^{-1})	**4.85 (3.71-6.66)**
R_{Coll} Hyperaemia† (mmHg · cm^{-1} · s^{-1})	**4.94 (2.88-7.77)**
R_P Hyperaemia† (mmHg · cm^{-1} · s^{-1})	**3.39 (2.09-5.26)**
Δcombined non-target vessel baseline flow§ (ml· min^{-1})	**-53.7±117.8**
Δcombined non-target vessel hyperaemic flow§ (ml· min^{-1})	**-37.2±106.0**

*n=28, †n=27, §n=32; FFRcoll indicates Fractional collateral flow reserve; CollFVR, collateral flow velocity reserve; R_{Coll}, resistance of the collateral vessel; R_P, resistance in the collateral recipient vessel downstream of the collateral supply.

Figures
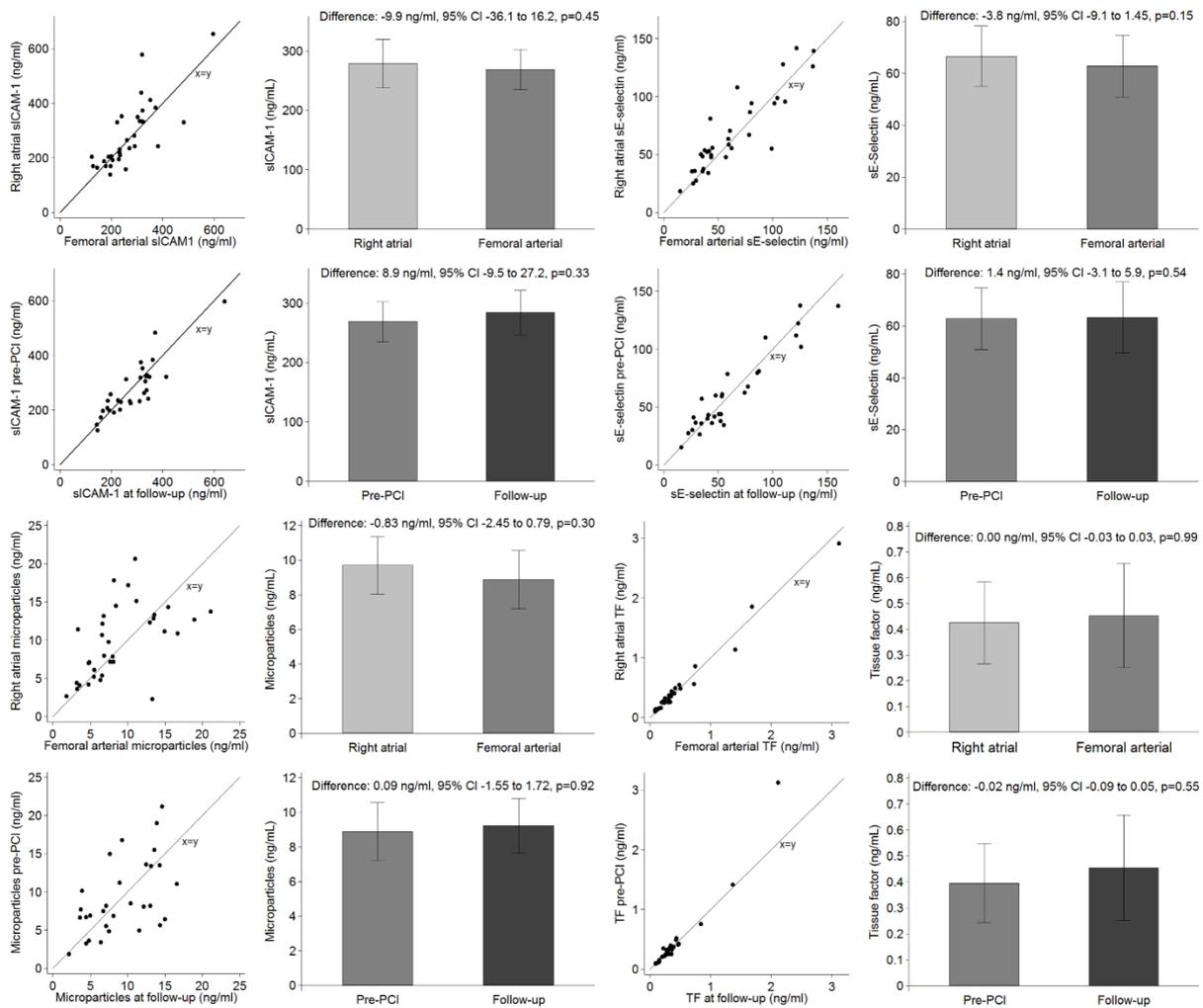
Figure 1. Comparison of right atrial with femoral arterial biomarker levels pre-PCI, and pre-PCI biomarker levels (Femoral arterial) with levels at follow-up (peripheral venous). Top left: sICAM-1, top right: sE-Selectin, bottom left: microparticles, bottom right: tissue factor (TF).
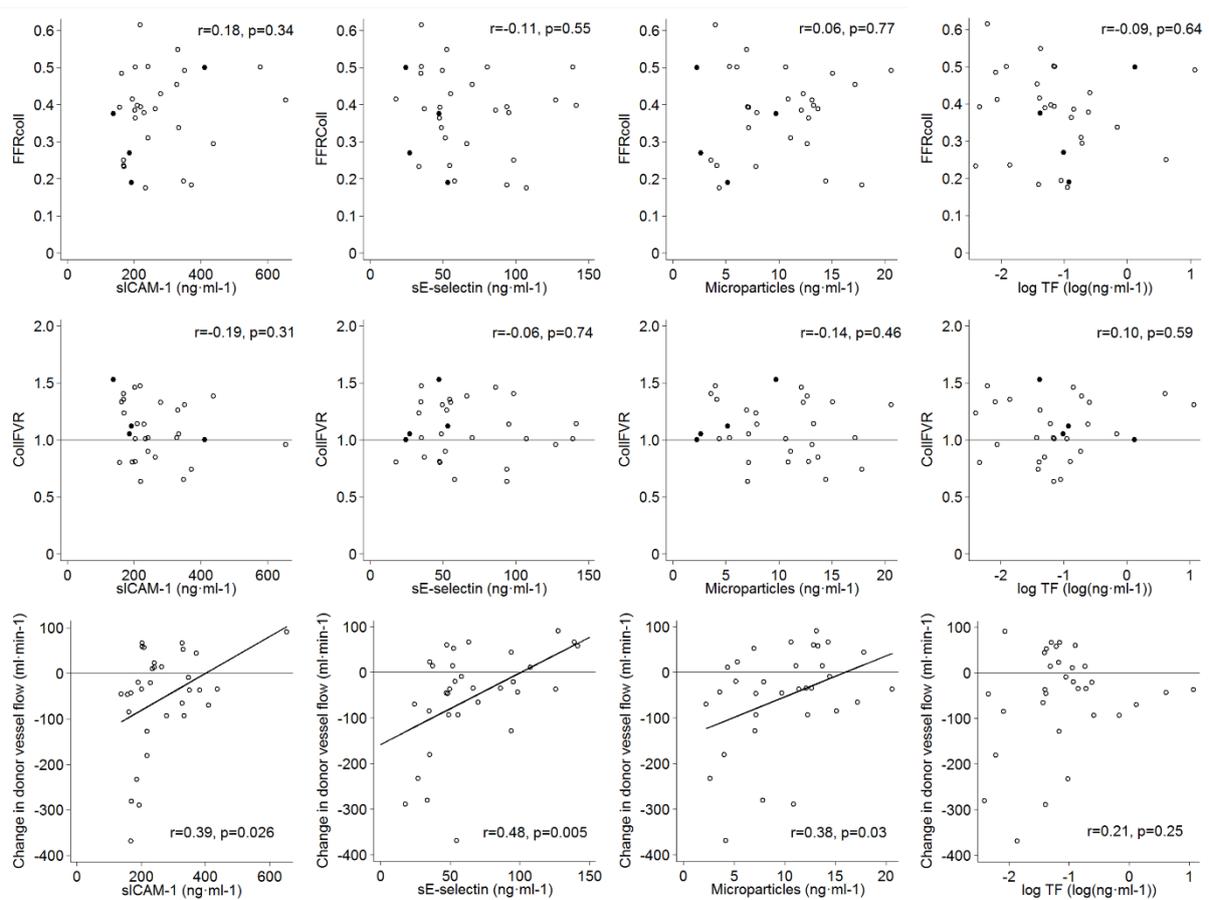
Figure 2. Relationships between biomarkers levels measured in the right atrium prior to PCI: sICAM-1, sE-Selectin, microparticles and tissue factor (TF); and measures of collateral perfusion: fractional collateral flow reserve(FFRcoll, n=31), Collateral flow velocity reserve (CollFVR, n=30), and summed change in absolute baseline flow, adjusted for rate pressure product after CTO PCI (n=32). TF levels are transformed logarithmically. Solid markers represent measures taken by a retrograde approach.

Disclosures

The authors declare that they have no conflict of interest.

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