

Tumour necrosis factor α concentration and collateral flow in patients with coronary artery disease and normal systolic left ventricular function

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Increased expression of tumour necrosis factor α (TNF α) has been found in cardiac tissue of patients with chronic heart failure, and the failing heart has been suggested as the cause of immune activation.¹

Another, less frequently reported facet of the macrophage derived mediator TNF α is its function as an angiogenic factor² which may be induced by myocardial ischaemia. This pleiotropic cytokine appears to act also as an angioinhibitory factor depending on the concentration, location, and duration of its action.³ So far, there have been no studies in patients with coronary artery disease (CAD) investigating the relation between the potentially angiogenic TNF α and directly measured collateral flow, the latter representing a variable in the course of CAD with considerable impact on its outcome.

The purpose of this study was to test the hypothesis that there is an association between TNF α and collateral flow in patients with CAD and normal systolic ventricular function.

METHODS

Patients

One hundred patients (mean (SD) age 65 (11) years, 70 men, 30 women) with one vessel and two vessel CAD were included in the study. All underwent percutaneous transluminal coronary angioplasty (PTCA) of one stenotic lesion because of symptoms related to stable CAD. Patients were prospectively selected on the basis of the following criteria: (1) no previous infarction in the myocardial area undergoing PTCA; (2) normal left ventricular ejection fraction; (3) no congestive heart failure; (4) no baseline ECG ST segment abnormalities; (5) no clinical or laboratory signs of inflammatory illness; (6) absence of overt neoplastic disease; and (7) no chronic obstructive pulmonary disease. The study population was divided into two groups according to the presence (insufficient collaterals, $n = 78$) or absence (sufficient collaterals, $n = 22$) of intracoronary ECG signs of myocardial ischaemia during the first one minute balloon occlusion of the stenosis to be revascularised.

The present investigation was approved by the institutional ethics committee, and the patients gave informed consent to participate in the study.

Coronary collateral assessment

In all study patients, coronary collateral flow relative to normal antegrade flow through the non-occluded coronary artery (collateral flow index (CFI)) was determined using coronary pressure measurements. A 0.014 inch pressure monitoring PTCA guidewire (Pressure Wave, Jomed, Switzerland) was set at zero, calibrated, advanced through the guiding catheter, and positioned distal to the stenosis to be dilated. CFI was determined by simultaneous measurement of mean aortic pressure (P_{ao} , mm Hg, via the angioplasty guiding catheter), the distal coronary artery pressure during balloon occlusion (P_{occl} , mm Hg), and the central venous pressure (CVP, mm Hg, via a right atrial catheter). CFI was calculated as:

$$[P_{occl} - CVP]/[P_{ao} - CVP].^4$$

Determination of TNF α

The blood samples obtained simultaneously with the CFI measurement from the ostium of the vessel (10 ml) were collected in sterile tubes (anticoagulant: sodium citrate), placed on ice, treated by centrifugation at 3000 *g* for 15 minutes at 4°C, and the plasma was frozen at -70°C. Plasma concentrations of TNF α were measured by an enzyme linked immunosorbent assay with a monoclonal antibody specific for TNF α (Biosource International, Camarillo, California, USA). The sensitivity of the test is equivalent to TNF α > 1 pg/ml.

RESULTS

Patient characteristics and clinical data

There were no significant differences between the two study groups regarding age of the patients, sex, body mass index, heart rate, and mean blood pressure before PTCA, or left ventricular ejection fraction and filling pressure. Also, there were no significant differences in the frequency of cardiovascular risk factors, recent non-Q wave myocardial infarctions, and the use of aspirin or vasoactive drugs.

TNF α concentration and coronary collateral flow data

Several variables for the assessment of the collateral circulation were significantly different among the groups (table 1).

TNF α values were found at detectable plasma concentrations (> 1 pg/ml) in 47% of all patients. Detectable TNF α concentrations were measured significantly more often in patients with insufficient collaterals than in those with sufficient collaterals, and TNF α concentrations were higher in the former group of patients than the latter (table 1).

There was a significant, inverse correlation between plasma TNF α concentrations and CFI values; this was the case for the entire study group (CFI = 0.23-0.004 TNF α ; $r = -0.21$, $p = 0.04$) as well as for patients having detectable (> 1 pg/ml) TNF α concentrations (CFI = 0.25-0.001 TNF α ; $r = -0.35$, $p = 0.02$).

DISCUSSION

This study in patients with CAD and normal systolic left ventricular function documents that serum TNF α was detectable in almost half the individuals investigated, and that TNF α was inversely related to simultaneously measured coronary collateral flow.

Abbreviations: CAD, coronary artery disease; CFI, collateral flow index; CVP, central venous pressure; P_{ao} , mean aortic pressure; P_{occl} , coronary artery pressure during balloon occlusion; PTCA, percutaneous transluminal coronary angioplasty; TNF α , tumour necrosis factor α

Table 1 Coronary angiographic and collateral data, TNF α

	Insufficient collaterals	Sufficient collaterals	p Value
Number of patients	78	22	
Coronary angiography			
One/two vessel disease	59%/41%	62%/38%	NS
Number of vessels diseased	1.7 (0.7)	1.8 (0.8)	NS
Vessel (PTCA): LAD/LCX/RCA	55%/15%/30%	23%/68%/9%	0.06
Diameter stenosis (%)	75 (15)	87 (11)	0.001
Collateral assessment			
Angiographic degree (before occlusion, 0–3)	0.4 (0.7)	1.3 (1.1)	0.0001
Angina pectoris during PTCA	6 (7%)	6 (27%)	0.001
Collateral flow index (no unit)	0.17 (0.12)	0.34 (0.15)	0.0001
TNF α detectable (> 1 pg/ml)	41 (53%)	6 (27%)	0.03
TNF α (pg/ml)	30.3 (79.7)	1.9 (6.5)	<0.05

Data presented as mean (SD) unless otherwise indicated.

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; NS, not significant; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; TNF α , tumour necrosis factor α .

TNF α in patients without congestive heart failure

In 1996, Torre-Amione and colleagues demonstrated that the non-failing human heart does not express TNF α , whereas the end stage failing human heart re-expresses large amounts of protein.¹ Conversely, our study in patients with CAD and stable angina pectoris, but with entirely normal systolic function, found detectable TNF α concentrations in 47% of patients.

TNF α as angiogenic or angioinhibitory factor

The present work provides several independent lines of evidence for the existence of an inverse relation between TNF α and collateral flow: (a) using a dichotomous, ECG based characterisation of coronary collaterals, the detectability of TNF α occurs in approximately half the patients with insufficient collaterals and in only one fourth of the individuals with collaterals sufficient to prevent myocardial ischaemia during vessel occlusion; (b) continuous TNF α values in all patients are also significantly different between the two collateral groups; and (c) using continuous measurements for both variables, TNF α and collateral flow, there is an inverse association irrespective of whether all or just the detectable values (> 1 pg/ml) are analysed. Our study was not designed to elucidate whether this inverse relation between intracoronary TNF α and directly and simultaneously measured collateral flow is causal, whether it reflects an angiogenic action of the cytokine with consequent feedback suppression of TNF α production, whether TNF α elicits angioinhibitory properties on the coronary circulation, or whether TNF α is upregulated very swiftly in patients with poorly developed collaterals in response to myocardial ischaemia even during a coronary occlusion as brief as one minute.

TNF α has been documented to induce capillary vessel formation in the rat cornea and the chick chorioallantoic membrane at low doses.² In vitro, TNF α has been shown to stimulate chemotaxis of bovine capillary endothelial cells and to induce these cells to form capillary tube-like structures.² Considering the above mentioned experimental work, it can be speculated that the inverse relation between TNF α and collateral flow index found in the present study reflects a situation whereby augmented expression of TNF α is needed in patients with poorly grown collaterals, and it is downregulated in patients with sufficient collaterals.

In vitro data documenting angioinhibitory properties of TNF α would allow an opposite interpretation of our data to the one outlined above⁵: the predominantly elevated TNF α concentrations in patients with low collateral flow reflect the ongoing inhibitory action of the cytokine on collateral development.

De novo production of TNF α in response to the very brief ischaemic stimulus used in our study is an unlikely explanation for the raised TNF α concentrations in patients with collaterals insufficient to prevent ischaemia. This is because blood samples for TNF α determination were collected simultaneously with, and not after, the collateral flow measurements during which the occlusion occurred.

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