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Coronary artery ectasia is related to coronary slow flow and inflammatory activation

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ABSTRACT

Aim: To evaluate possible links between coronary flow anomalies, inflammatory activation and coronary artery ectasia (CAE).
Methods: Fourteen consecutive patients with CAE diagnosed at coronary angiography were enrolled in the study and compared with 17 patients with coronary atherosclerosis without CAE and 15 controls with normal coronary angiography. All patients underwent blood assay with evaluation of circulating levels of interleukin (IL)-1b, IL-2, IL-8, IL-10 and tumor-necrosis-factor(TNF)-α. The number of coronary segments showing CAE at coronary angiography, the Markis class, and coronary flow assessed with TIMI frame count (TFC) were also assessed.
Results: Subjects with CAE showed higher levels of IL-1b, TNF-α, and IL-10 ($p < 0.05$).
The number of coronary segments showing CAE was related to TFC both in left anterior descending (LAD) coronary artery ($p < 0.01$) and in right coronary artery (RCA) ($p < 0.001$), and to circulating levels of IL-1b and IL-10 ($p < 0.01$). TFC on LAD ($p < 0.05$) and on RCA ($p < 0.001$), circulating IL-1b levels ($p < 0.01$), IL-8 ($p < 0.05$), and IL-10 ($p < 0.01$) were proportionally increased comparing controls, subjects with coronary atherosclerosis without CAE, and with decreasing Markis class.
In subjects with CAE involving LAD, TFC on LAD was related to IL-8 and TNF-α levels ($p < 0.05$); subjects with IL-1b levels above median showed higher TFC values on LAD ($p < 0.01$),
Conclusions: In subjects with CAE, the extension of disease is related to the impairment of coronary circulation and to inflammatory activation. The inflammatory response is also related to an impaired coronary circulation.

1. Background

Etiology and progression of atherosclerosis are characterized by the activation of inflammatory mechanisms [1,2]; also coronary complications of atherosclerosis may present with an inflammatory activation [3–5]. Increased levels of C-reactive protein (CRP) and acute phase proteins are detectable in the acute phase of acute myocardial infarction (AMI) and may predict the risk of future adverse events [3,6].

Coronary artery ectasia (CAE), a variant of coronary atherosclerosis characterized by ectatic coronary segments, has been found in a large series of coronary angiographies from the Coronary Artery Surgery Study (CASS) registry in 4.9% of more than 20,000 coronary angiograms reviewed [7].

There is evidence that CAE may be linked with an inflammatory activation [8–10]. Moreover, even anomalies in coronary flow, detectable in CAE [11], may be related to increased circulating levels of inflammatory markers [12].

We therefore sought to evaluate further possible links between coronary flow anomalies, inflammatory activation and CAE.

2. Methods

Fourteen consecutive patients with CAE diagnosed at coronary angiography were enrolled in the study and compared with 17 patients with coronary atherosclerosis without CAE and 15 controls with normal coronary angiography.

CAE was defined as the diameter of the ectatic segment being more than 1.5 times larger compared with an adjacent healthy reference segment [7,13], as in prior studies.

All patients underwent blood assay with evaluation of circulating levels of interleukin (IL)-1b, IL-2, IL-8, IL-10 and tumor-necrosis-factor (TNF)-α.

For each patient the number of coronary segments with signs of CAE at coronary angiography, Markis class [14], and coronary

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flow assessed with TIMI frame count [15] were also assessed. Left ventricular ejection fraction was measured by 2D echocardio graphy.

Subjects with acute coronary syndrome within one month or chronic total coronary occlusion were excluded from the study. Patients with chronic inflammatory or neoplastic disease, recent infectious disease, fever, immunosuppressive drug therapy, or immunologic disorder were also excluded from the study.

2.1. Cytokines

Blood samples for cytokines analysis were immediately centrifuged and serum separated after coagulum retraction by centrifugation at 2000 rpm for 10 min; it was then frozen at −20 °C until laboratory assay. All cytokines were standardized by inclusion of a titration of the appropriate purified recombinant cytokines of known concentration. Normal values, provided by furnisher (Immulite, Siemens, Deerfield, IL, USA), were <5 pg/mL for IL-1b, <62 pg/mL for IL-8, <1.8 pg/mL for IL-10, and <8.1 pg/mL for TNF-α.

3. Statistical analysis

The results were expressed as mean value ± standard deviation for continuous variable or percentage for dichotomic variable. Variables were tested for normality with Kolmogorov–Smirnov and Lilliefors and compared with Student's *t* test, Mann–Whitney *U*-test, or χ^2 test as required.

Correlations were analyzed using Pearson's or Spearman correlation test as required. Entered and stepwise multiple regression analysis was used to analyze variables affecting cytokines levels, including confounding factors such as age and gender. A $p < 0.05$ was considered as statistically significant.

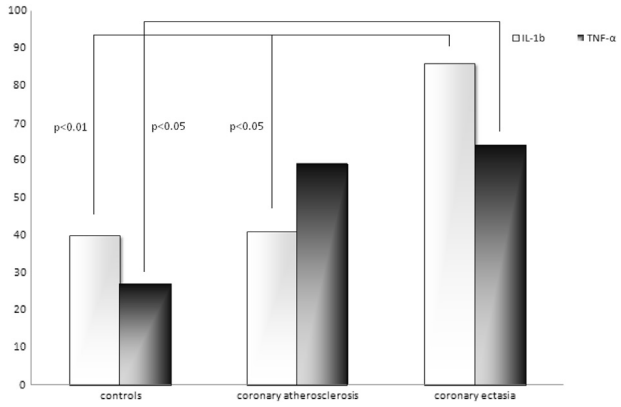

Fig. 1. Increasing rates of subjects with circulating levels of IL-1b and TNF-α above upper level of normal with coronary atherosclerosis and coronary artery ectasia (*p* for trend <0.05).

4. Results

Population's characteristics are given in Table 1. Markis class IV CAE was found in 42.9% of subjects with CAE, class III in 21.4%, class II in 28.6%, and class I in 7.1%.

The CAE group showed higher rates of subjects with circulating levels of IL-1b ($r = 0.36$, p for trend < 0.05, Fig. 1) and TNF-α ($r = 0.30$, $p < 0.05$, Fig. 1) above upper level of normal (ULN) and higher circulating levels of IL-10 ($p < 0.05$, Fig. 2) in comparison to coronary atherosclerosis without CAE group and controls: the number of circulating IL levels above median was proportionally increased as well ($r = 0.38$, $p < 0.05$). Correlation with IL-10 remained significant even after correction for age and gender.

Table 1
General characteristics of population.

	Mean ± SD	Mean ± SD	Mean ± SD	*p*	Mean ± SD	*p*	*p*
	Entire population ($N = 46$)	Controls ($N = 15$)	Coronary artery disease ($N = 17$)	vs. controls	Coronary artery ectasia ($N = 14$)	vs. controls	vs. CAD
Gender	80%	47%	94%	<0.01	100%	<0.001	n.s.
Age	61.8 ± 9.1	62.3 ± 8.8	64.3 ± 10.6	n.s.	58.3 ± 6.6	n.s.	n.s.
Diabetes	20%	20%	24%	n.s.	14%	n.s.	n.s.
Dislipidemia	67%	33%	94%	<0.001	71%	<0.05	n.s.
Hypertension	85%	67%	100%	<0.01	86%	n.s.	n.s.
LVEF	50.3 ± 8.5	52.2 ± 9.7	49.4 ± 7.4	n.s.	49.0 ± 9.3	n.s.	n.s.
TFC on LAD	12.8 ± 3.6	12.1 ± 3.7	12.2 ± 3.4	n.s.	14.3 ± 3.3	n.s.	n.s.
TFC on RC	14.9 ± 7.4	11.1 ± 2.9	13.3 ± 5.3	n.s.	20.9 ± 9.3	<0.001	<0.01
CAE on right coronary					93%		
CAE on left coronary					36%		
Total # of CAE segment					2.1 ± 1.2		
Markis class					2.0 ± 1.0		
IL-1b	8.1 ± 32.9	2.2 ± 2.9	2.4 ± 3.0	n.s.	21.4 ± 58.7	n.s.	n.s.
IL-1b >ULN	54%	40%	41%	n.s.	86%	<0.01	<0.05
IL-8	1112.4 ± 2159.7	838.6 ± 1941.5	953.0 ± 1912.7	n.s.	1599.2 ± 2685.0	n.s.	n.s.
IL-8 >ULN	52%	40%	59%	n.s.	57%	n.s.	n.s.
IL-10	3.0 ± 3.0	2.0 ± 2.5	2.1 ± 2.5	n.s.	5.3 ± 2.8	<0.01	<0.01
IL-10 >ULN	57%	40%	41%	n.s.	93%	<0.01	<0.01
TNF-α	11.2 ± 4.2	10.6 ± 4.2	11.4 ± 4.9	n.s.	11.7 ± 3.5	n.s.	n.s.
TNF-α >ULN	50%	27%	59%	n.s.	64%	<0.05	n.s.
Number of markers >ULN	4.2 ± 2.1	2.9 ± 2.2	5.3 ± 1.7	<0.05	4.7 ± 1.5	<0.05	n.s.
β-blockers	43%	33%	47%	n.s.	50%	n.s.	n.s.
Statins	39%	20%	59%	<0.05	36%	n.s.	n.s.
ACE-inhibitors	36%	13%	50%	<0.05	43%	n.s.	n.s.
ARB	22%	13%	31%	n.s.	21%	n.s.	n.s.
Anti-platelet drugs	77%	60%	93%	<0.05	79%	n.s.	n.s.

Abbreviations: LVEF: left ventricular ejection fraction; TFC: TIMI frame count; LAD: left anterior descending coronary artery; RC: right coronary artery; CAE: coronary artery ectasia; ULN: upper level of normal; ACE: angiotensin converting enzyme; and ARB: angiotensin receptor blockers.