Sites of Interleukin-6 Release in Patients With Acute Coronary Syndromes and in Patients With Congestive Heart Failure

Efthymios N. Deliargyris, MD, Ronald J. Raymond, MD, Theoharis C. Theoharides, MD, PhD, William S. Boucher, B.Pharm, David A. Tate, MD, and Gregory J. Dehmer, MD

This study examines the source of elevated interleukin-6 (IL-6) levels in patients with acute coronary syndrome (ACS) and congestive heart failure (CHF). IL-6 is elevated in the peripheral blood of patients with ACS and CHF, but it is not known if this proinflammatory cytokine is from a cardiac or extracardiac source. Blood samples were obtained from the femoral artery, femoral vein, left main coronary artery, and coronary sinus in 57 patients during cardiac catheterization. IL-6 levels from 12 patients with ACS and 12 patients with CHF were compared with the IL-6 levels in 33 patients who had neither of these clinical conditions. Median IL-6 levels in the peripheral and coronary circulation were a minimum fivefold higher in patients with ACS or CHF relative to control patients. An elevated transcardiac IL-6 gradient (coronary sinus–left main level) was present in patients with ACS (median 5.2; 25th and 75th percentiles 3.9 and 29.3 pg/ml, respectively) compared with control patients (median 0, −0.7 and 0.5 pg/ml; p <0.001), but not in patients with CHF (median 0.4, −0.7 and 3.5 pg/ml; p = NS). Elevated IL-6 levels in patients with ACS derive from a cardiac source, presumably from "inflamed" coronary plaques and areas of myocardial necrosis, whereas elevated levels in patients with CHF are most likely the result of extracardiac production.

(Am J Cardiol 2000;86:913–918)

The role of inflammation in the development, progression, and destabilization of coronary artery disease is becoming increasingly recognized.[1–6] Patients with an acute coronary syndrome (ACS), including unstable angina, non-Q and Q-wave myocardial infarction, have elevated levels of acute-phase reactants such as C-reactive protein, serum amyloid A protein, and fibrinogen. Importantly, when elevated these inflammatory markers correlate well with the risk of recurrent events, suggesting an etiologic role for inflammation in the process of plaque destabilization.[7–9] The hepatic production of such acute-phase reactants is regulated by proinflammatory cytokines, predominantly interleukin-6 (IL-6), which is also elevated in the setting of ACS.[10–12] The source of IL-6 in patients with ACS, however, remains unknown. A systemic inflammatory response has also been demonstrated in patients with congestive heart failure (CHF) and is linked to poor prognosis.[13–16] IL-6 levels are elevated in patients with CHF irrespective of an ischemic or nonischemic etiology, suggesting a different mechanism and possibly a different site of production of this cytokine than in patients with ACS.[17,18] We hypothesized that elevated IL-6 levels in patients with ACS are the result of cardiac release into the coronary circulation, whereas elevated IL-6 levels in patients with CHF represent a systemic release secondary to peripheral tissue hypoperfusion. To test this hypothesis, we measured IL-6 levels in both the peripheral and coronary circulations of patients with ACS, CHF, and in patients with neither of these clinical conditions.

METHODS

Patient selection: Patients were identified for study from those referred for cardiac catheterization for typical clinical indications. There were no specific inclusion criteria other than a willingness to provide informed consent. Patients with a history of cardiac transplantation or coronary artery bypass surgery were excluded, because the pathophysiology of venous graft and allograft vasculopathy is considered different from native coronary artery disease. Patients receiving corticosteroid therapy were also excluded. The protocol was approved by the institutional review board of the medical school.

Definitions: Patients were considered to have an ACS if they presented with a Q-wave myocardial infarction, non–Q-wave myocardial infarction or unstable angina. Q-wave myocardial infarction was defined by the presence of (1) chest pain typical for myocardial ischemia lasting >30 minutes, (2) eleva-

From the Cardiac Catheterization Laboratory at the University of North Carolina Hospitals, Chapel Hill, North Carolina; and the Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, Massachusetts. This work was funded, in part, by a Young Investigator Grant from Merck & Co. Inc., West Point, Pennsylvania; and the Bracco Diagnostics, Inc., Princeton, New Jersey; and Society for Cardiac Angiography and Interventions Fellowship Program for Research in Cardiac Imaging and Invasive Cardiology to Dr. Deliargyris, and a grant from Kos Pharmaceuticals, Miami, Florida, to Dr. Theoharides. Manuscript received February 14, 2000; revised manuscript received and accepted May 2, 2000.

Address for reprints: Gregory J. Dehmer, MD, Cardiac Catheterization Laboratory, Administrative Offices, Room 2227, UNC Hospitals, 101 Manning Drive, Chapel Hill, North Carolina 27514. E-mail: dehmer@unch.unc.edu.

0002-9149/00/$–see front matter
PII S0002-9149(00)01121-8

tion of the total creatine kinase to at least twice the upper limit of normal with an elevated creatine kinase-MB fraction, and (3) development of diagnostic Q waves in ≥2 electrically contiguous leads. Non–Q-wave myocardial infarction was defined in the same manner, but without the appearance of new Q waves. Unstable angina was defined in a standard fashion.[19] Patients were considered to have CHF if they presented with clinical and radiographic signs of pulmonary edema or had a documented history of CHF. All patients with CHF were treated and compensated (New York Heart Association class II or III) at the time of sample collection. The transcardiac gradient was defined as the coronary sinus–left main IL-6 level in picograms per milliliter.

Sample collection and analysis: Cardiac catheterization, left ventriculography, and coronary angiography were performed in a standard fashion. Samples were obtained from the femoral artery and femoral vein after sheath insertion. Coronary sinus cannulation was performed from the femoral vein with a Simmons II catheter (Cook, Inc., Bloomington, Indiana) as previously described,[20] and when necessary, confirmed by oxygen saturation measurement. The left main coronary artery was cannulated, usually with a Judkins catheter. Simultaneously, samples were obtained from the left main and coronary sinus before coronary angiography. Blood samples were allowed to clot and then centrifuged at room temperature for 5 minutes. The serum was separated and immediately frozen at −80°C. At a later date, samples were shipped in dry ice to the Department of Pharmacology and Experimental Therapeutics of Tufts University, Boston, Massachusetts, for analysis. IL-6 measurements were obtained by enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, Minnesota) and levels expressed in picograms per milliliter.

Angiography: Biplane left ventriculography was performed in a 50° left anterior oblique and 30° right anterior oblique projection. Left ventricular volumes and ejection fractions were calculated by the biplane area-length method using the Wynne regression formula.[21] Coronary angiography was performed in multiple right and left anterior oblique projections with cranial and caudal angulation for visualization of all segments of the coronary arteries. Coronary artery disease was considered present if there was a stenosis diameter narrowing ≥50% in at least 1 of the 3 major epicardial coronary arteries. Stenosis severity was determined by the consensus reading of 2 experienced observers.

Statistical analysis: Baseline characteristics are expressed as mean ± SD for continuous variables and as percentages for categorical variables. Because of extremely elevated IL-6 levels in certain patients, some data groups were not normally distributed. IL-6 values are therefore expressed as medians with 25th and 75th percentiles, and nonparametric tests (Kruskal-Wallis and Dunn's test) were used to evaluate these data. For normally distributed data, an analysis of variance followed by the Newman-Keuls test was used for differences among groups. Chi-square analysis or Fisher's exact test, where appropriate, were used for categorical variables. Analyses were performed using SPSS 8.0 statistical software (SPSS, Inc. Chicago, Illinois). A p value <0.05 was considered significant.

RESULTS

Patients: Of the 57 patients studied, 42 were men and 15 were women (mean age 59 ± 14 years). Twelve patients had ACS: 3 with Q-wave acute myocardial infarction, 3 with non–Q-wave acute myocardial infarction, and 6 with unstable angina pectoris. None of the patients with an ACS had CHF. There were 12 patients with CHF: 10 had pulmonary edema and 2 had a history of CHF. The indication for catheterization in all patients with CHF was to determine if coronary artery disease was the underlying etiology of their CHF. Six patients had ischemic cardiomyopathy based on the presence of significant coronary artery disease, and the remaining 6 did not have coronary, valvular, or myocardial infiltrative disease and were considered to have idiopathic dilated cardiomyopathy. Furthermore, based on clinical and electrocardiographic criteria along with serial myocardial enzyme measurements, none of the patients with CHF had evidence of ongoing myocardial ischemia. The remaining 33 patients, who had neither ACS nor CHF, formed the control group. In the control group, 52% had ≥1 coronary stenosis of ≥50% diameter narrowing. The control group was selected for catheterization if they had the following clinical indications: chronic stable angina (15 patients), atypical chest pain but an abnormal stress test (14 patients), syncope (2 patients), and asymptomatic but an abnormal stress test as part of their preoperative evaluation for renal transplantation (2 patients). Compared with the control group, patients with ACS had similar clinical characteristics, but, as expected, had a higher incidence of coronary artery disease (Table 1). Patients with an ACS also had higher erythrocyte sedimentation rates and leukocyte counts than control patients, and were more frequently treated with aspirin. Not surprisingly, patients in the CHF group had a significantly lower mean left ventricular ejection fraction than controls and were more frequently treated with angiotensin-converting enzyme inhibitors and digitalis.

IL-6 levels: Median values with their 25th and 75th percentiles for IL-6 levels obtained from the 4 sampling sites in all patient groups are listed in Table 2. Compared with the control group, median IL-6 values were at least fivefold higher at each of the sampling sites in patients with ACS or CHF. Both femoral artery and vein IL-6 levels were higher in those with ACS than in the control group, and tended to be higher in those with CHF than in the control group (Table 2, Figure 1). In the peripheral circulation, there was no difference in IL-6 levels between the femoral artery and femoral vein in any of the groups. Both the ACS and CHF groups also had higher IL-6 levels in the coronary circulation than the control group (Table 2, Figure 2). In contrast to the peripheral circulation, however, there was a significant "step-up" in IL-6 levels between the left main and the coronary sinus in

TABLE 1 Clinical Characteristics for All Patient Groups

	Acute Coronary Syndrome (n = 12)	p Value	Controls (n = 33)	p Value	Congestive Heart Failure (n = 12)
Age (yrs)	60 ± 8	0.84	60 ± 13	0.38	56 ± 19
Men	10/12 (83%)	0.70	24/33 (73%)	0.72	8/12 (67%)
White (%)	10/12 (83%)	0.46	22/33 (67%)	1.0	8/12 (67%)
ACE-I use	1/12 (8%)	0.40	8/33 (24%)	0.014	8/12 (67%)
Creatinine (mg/dl)	1.0 ± 0.2	0.20	1.2 ± 0.9	0.90	1.1 ± 0.3
β blockers	8/12 (67%)	0.30	16/17 (48%)	0.20	3/12 (25%)
Digitalis	0/12 (0%)	1.0	2/33 (6%)	0.001	8/12 (75%)
Aspirin	12/12 (100%)	0.04	23/33 (70%)	1.0	9/12 (75%)
CAD	11/12 (92%)	0.02	17/33 (52%)	0.93	6/12 (50%)
Diabetes mellitus	2/12 (33%)	0.45	7/33 (21%)	0.25	5/12 (42%)
ESR (mm/h)	33 ± 21	0.01	18 ± 14	0.16	27 ± 27
Systemic hypertension	7/12 (58%)	0.50	23/33 (70%)	1.0	8/12 (67%)
LV ejection fraction	0.57 ± 0.11	0.33	0.61 ± 0.12	<0.001	0.30 ± 0.13
Cigarette smoking	6/12 (50%)	0.32	11/33 (33%)	0.32	6/12 (50%)
Leukocytes (10^9/L)	8.7 ± 1.9	0.004	6.5 ± 2.0	0.63	6.9 ± 2.1

ACE-I = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease; ESR = erythrocyte sedimentation rate; LV = left ventricular.

TABLE 2 Median IL-6 Levels (pg/ml) with 25th and 75th Percentiles in all Patient Groups

Sampling Site	Acute Coronary Syndromes (n = 12)	p Value	Controls (n = 33)	p Value	Congestive Heart Failure (n = 12)
Femoral vein					
Median	10.9	<0.001	1.0	<0.1	5.8
(25%–75%)	4.0–17.7		0–3.9		1.8–13.7
Femoral artery					
Median	10.4	<0.01	0.1	<0.1	3.9
(25%–75%)	2.1–12.9		0–3.8		0.9–9.3
Left main					
Median	10.1	<0.01	0.8	<0.01	6.4
(25%–75%)	2.1–13.2		0–3.2		2.9–12.0
Coronary sinus					
Median	15.2	<0.001	0.7	<0.01	7.6
(25%–75%)	7.3–64.0		0–3.6		4.3–14.0
Transcardiac gradient					
Median	5.2	<0.001	0.0	NS	0.4
(25%–75%)	3.9–29.3		−0.7–0.5		−0.7–3.5

the ACS group that was not present in either the CHF or control groups.

Transcardiac IL-6 gradient: The transcardiac gradient (Table 2, Figure 3) was increased in the ACS group compared with the other groups. Because the ACS group included patients with and without evidence of myocardial infarction, a subgroup analysis was performed based on the presence of elevated cardiac enzymes. Although not as large as the transcardiac gradient of the 6 patients with myocardial infarction, the transcardiac gradient in the 6 patients with unstable angina was still significantly greater than that derived in the control group ($p = 0.04$, Figure 4).

Coronary artery disease and IL-6 levels: The presence of coronary artery disease alone was not associated with higher IL-6 levels. Among the 33 patients in the control group, 17 (52%) had significant coronary artery disease. There were no differences in IL-6 levels at any of the sampling sites among patients with or without coronary artery disease (Table 3). Similarly, the transcardiac IL-6 gradient was low and similar in both patients with and without coronary artery disease (p = NS for all comparisons between the 2 groups).

DISCUSSION

Our findings of elevated circulating IL-6 levels in patients with ACS and CHF add to the existing reports linking ongoing inflammation with these 2 distinct clinical conditions.[1–18] In our study, however, by obtaining samples from the peripheral and the coronary circulation, we were able to demonstrate different sites of IL-6 production among patients with ACS and CHF.

IL-6 production in acute coronary syndromes: Our patients with ACS had elevated peripheral IL-6 levels that were similar in magnitude to those reported in previous studies.[10–12] Furthermore, in our patients with ACS, we found higher IL-6 levels in the coronary sinus than in the left main artery, thereby resulting in an elevated transcardiac gradient that was not present in control or CHF patients. This pattern implies a release of IL-6 into the coronary circulation of patients

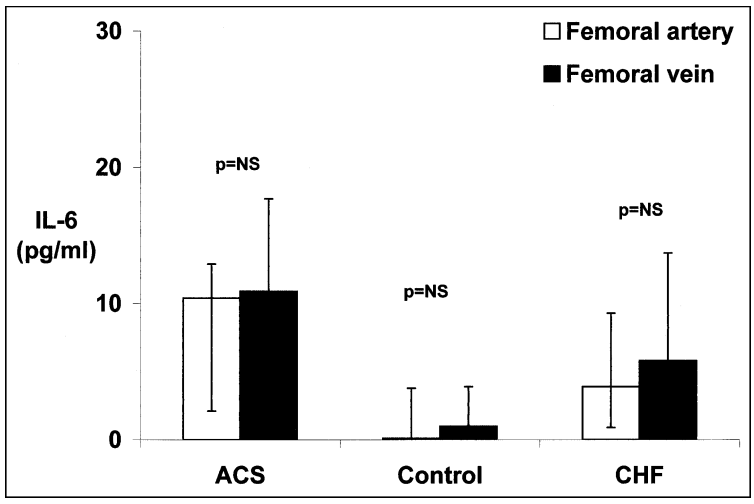

FIGURE 1. Interleukin-6 levels from the peripheral circulation. The *bar* indicates the median value and the *line* indicates the 25th and 75th percentiles. There were no differences between femoral artery and vein IL-6 levels within any group. Both femoral artery and vein IL-6 levels were higher in those with an ACS than in the control group ($p < 0.01$) and tended to be higher ($p < 0.1$) in those with CHF.

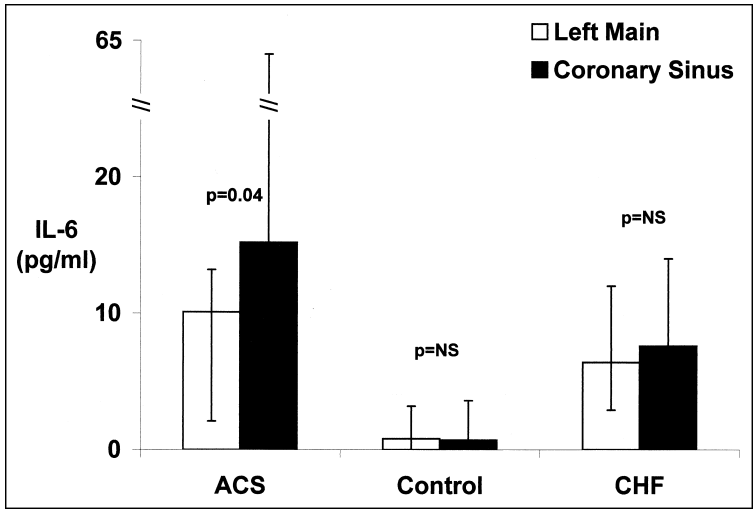

FIGURE 2. Interleukin-6 levels from the coronary circulation. The *bar* indicates the median value and the *line* indicates the 25th and 75th percentiles. IL-6 levels were higher in both the ACS and CHF groups ($p < 0.01$) than in the control group. In patients with ACS there was a significant "step-up" in IL-6 levels between the left main and coronary sinus ($p = 0.04$), which was not present in the CHF or the control group.

with ACS, either from the coronary vasculature or from the myocardium.

An elevated transcardiac gradient of IL-6 has previously been reported in patients with acute Q-wave myocardial infarction.[22] There are no studies measuring coronary sinus IL-6 levels in patients with unstable angina and non–Q-wave myocardial infarction. This is an important distinction because the mechanism of IL-6 production may be different in these patient populations. In the setting of a myocardial infarction, both myocardial necrosis and successful reperfusion appear to upregulate myocardial IL-6 production.[22–24] In our study a transcardiac IL-6 gradient was present in patients both with and without elevation in cardiac enzymes. Although smaller than in patients with an infarction, the presence of an increased transcardiac IL-6 gradient in patients with unstable angina suggests an additional mechanism besides myocardial necrosis contributing to cytokine production.

Histologic examination of plaques associated with ACS shows a pronounced local inflammatory response not present in plaques of patients with chronic stable angina.[6] The macrophages, T-lymphocytes, and mast cells present in these "inflamed" plaques are capable of producing proinflammatory cytokines such as IL-6, along with matrix-degrading enzymes leading to fibrous cap weakening and plaque rupture.[4–6,25,26] Ongoing plaque inflammation is probably responsible for the higher plaque temperatures recorded by Stefanadis et al[27] in patients with ACS than in patients with chronic stable coronary artery disease. Therefore, in the absence of myocardial necrosis, the observed transcardiac IL-6 gradient may be due to ongoing cytokine release from these "hot" and "unstable" coronary plaques. Such local cytokine release may help explain the rapid and occasionally multifocal disease progression observed after an acute myocardial infarction, even in areas distant from the culprit lesion.[28] IL-6 and other inflammatory mediators released from the culprit lesion during an ACS may initiate or exacerbate plaque inflammation throughout the coronary circulation, resulting in rapid disease progression and recurrent events.[9,10]

In our control group, there was no difference in IL-6 levels from any sampling site between those with and without coronary artery disease, suggesting that increased IL-6 production is not simply related to the presence of coronary atherosclerosis, but is specifically associated with the presence of an ACS.

IL-6 production in congestive heart failure: Elevated peripheral levels of cytokines, including IL-6, have been demonstrated in patients with CHF and are associated with a worse prognosis.[13–18] The exact site and mechanism of production is not known; however, because elevated cytokine levels are present in ischemic and nonischemic cardiomyopathies, it is unlikely that they are related to coronary artery disease.[13–18] In contrast, they seem to correlate well with the degree of neurohormonal activation that accompanies a low output state. It is therefore believed that these cytokines are the result of "peripheral spillover" from hypoperfused tissues. Similarly, our study patients with CHF also had elevated IL-6 levels irrespective of the presence of coronary disease. Furthermore, the absence of a transcar-

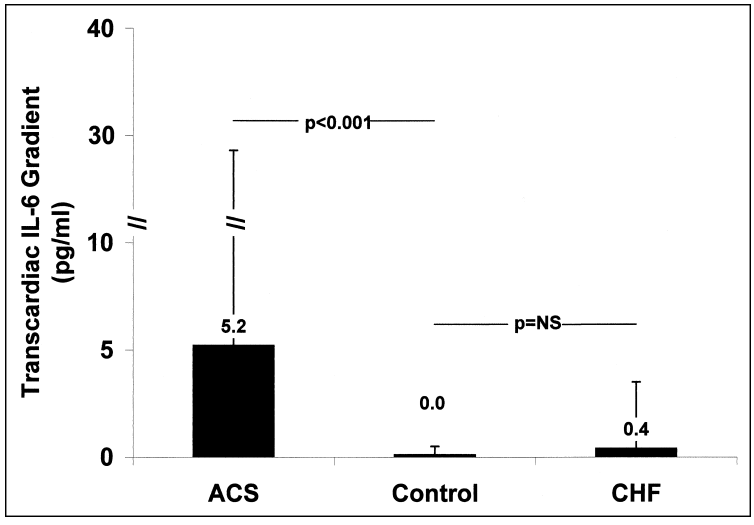

FIGURE 3. Transcardiac IL-6 gradients for all groups. The *bar* indicates the median value and the *line* indicates the 25th and 75th percentiles. Compared with the controls, those with ACS had a higher transcardiac gradient (p <0.001).

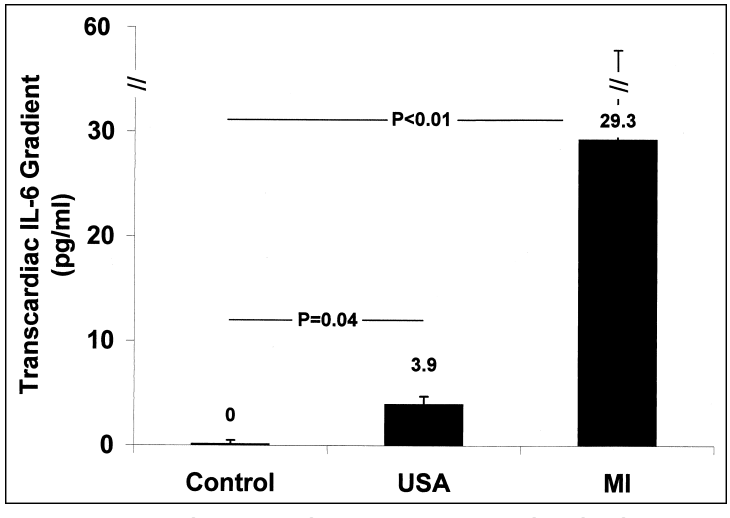

FIGURE 4. Transcardiac IL-6 gradient in ACS patients with and without evidence of infarction. The *bar* indicates median value and the *line* indicates the 25th and 75th percentiles. Compared with the control group, the transcardiac IL-6 gradient was increased in those with unstable angina (USA) (p <0.04) and in those with a recent myocardial infarction (MI) (p <0.01).

diac IL-6 gradient in our population with CHF supports the notion that elevated cytokine levels in CHF are the result of extracardiac production.

Study limitations: Although our data suggest that the source of IL-6 is different between patients with an ACS and those with CHF, there are several limitations to this interpretation. First, in patients with CHF, we cannot exclude the possibility of chronic "low-grade" IL-6 release from the myocardium, contributing to the elevated peripheral levels. Second, although our data show an elevated transcardiac gradient in patients with ACS, it is not possible to determine if the source of the IL-6 is solely from the myocardium, coronary vasculature, or some combination of both. Half of our patients with an ACS had no evidence of myocardial necrosis detected by total creatine kinase and creatine kinase-MB elevations. More sensitive markers of necrosis, such as troponins, could have been elevated in these patients. Third, there appears to be a time course for the release of IL-6 after the onset of an ACS.[10–12] Our samples were collected during cardiac catheterization that was performed from 1 hour after symptom onset in the setting of acute myocardial infarction and primary angioplasty to 1 week after presentation in some patients with unstable angina. Although the timing of sampling is probably important with regard to absolute IL-6 levels, it does not alter the substance of our findings, namely the presence of a transcardiac IL-6 gradient in most patients with ACS.

Acknowledgment: We acknowledge the invaluable support of the technical and nursing staff of the cardiac catheterization laboratory in the performance of this study. We also acknowledge Joseph Pye for his assistance in data analysis and presentation.

TABLE 3 Median IL-6 Levels (pg/ml) with 25th and 75th Percentiles in the Control Group Based on the Presence of Coronary Artery Disease

	Coronary Artery Disease Absent (n = 16)	Coronary Artery Disease Present (n = 17)
Femoral artery	0.52 0–3.0	1.3 0–5.6
Femoral vein	0.56 0–3.2	0.1 0–3.7
Left main	0.0 0–1.8	0.8 0–5.0
Coronary sinus	0.0 0–1.8	0.9 0–4.0
Transcardiac gradient	0.0 0–0.5	0 −0.9–0.1

1. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340: 115–126.
2. Lee RT, Libby P. The unstable atheroma. *Arterioscler Thromb Vasc Biol* 1997;17:1859–1867.
3. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non–Q-wave myocardial infarction. *Circulation* 1998;97:1195–1206.
4. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation* 1994;89:36–44.
5. Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 1995;92:1084–1088.
6. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. *Circulation* 1994;90:775–778.
7. Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease *Am J Cardiol* 1990;65:168–172.
8. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB,

Maseri A. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 1994;331:417–424.
9. Biasucci LM, Liuzzo G, Grillo RL, Caligiuri G, Rebuzi AG, Buffon A, Summaria F, Ginnetti F, Fadda G, Maseri A. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation* 1999;99:855–860.
10. Biasucci LM, Liuzzo G, Fantuzzi G, Caligiuri G, Rebuzzi AG, Ginnetti F, Dinarello CA, Maseri A. Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999;99:2079–2084.
11. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, Rebuzzi A, Ciliberto G, Maseri A. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;94:874–877.
12. Pannitteri G, Marino B, Campa PP, Martucci R, Testa U, Peschle C. Interleukins 6 and 8 as mediators of acute phase response in acute myocardial infarction. *Am J Cardiol* 1997;80:622–625.
13. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;323:236–241.
14. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996;27:1201–1206.
15. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, Mabuchi N, Sawaki M, Kinoshita M. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998;31:391–398.
16. MacGowan GA, Mann DL, Kormos RL, Feldman AM, Murali S. Circulating interleukin-6 in severe heart failure. *Am J Cardiol* 1997;79:1128–1131.
17. Roig E, Orus J, Pare C, Azqueta M, Filella X, Perez-Villa F, Heras M, Sanz G. Serum interleukin-6 in congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1998;82:688–690.
18. Munger MA, Johnson B, Amber IJ, Callahan KS, Gilbert EM. Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1996;77:723–727.
19. Braunwald E. Unstable angina. A classification. *Circulation* 1989;80:410–444.
20. Dehmer GJ, Schmitz JM, Malloy CR. A new technique for cannulation of the coronary sinus from the femoral vein. *Cathet Cardiovasc Diagn* 1986;12:426–429.
21. Wynne J, Green LH, Mann T, Levin D, Grossman W. Estimation of left ventricular volumes in man from biplane cineangiograms filmed in oblique projections. *Am J Cardiol* 1978;41:726–732.
22. Neumann FJ, Ott I, Gawaz M, Richardt G, Holzapfel H, Jochum M, Schomig A. Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. *Circulation* 1995;92:748–755.
23. Yamauchi-Takihara K, Ihara Y, Ogata A, Yoshizaki K, Azuma J, Kishimoto T. Hypoxic stress induces cardiac myocyte-derived interleukin-6. *Circulation* 1995;91:1520–1524.
24. Seino Y, Setsuta K, Tomita Y, Nejima J, Takano T, Hayakawa H. Increased plasma levels of interleukin-6 and myocardial stunning after coronary reperfusion therapy. *Am J Cardiol* 1995;76:718–720.
25. Wesley RB II, Meng X, Godin D, Galis ZS. Extracellular matrix modulates macrophage functions characteristic to atheroma: collagen type I enhances acquisition of resident macrophage traits by human peripheral blood monocytes in vitro. *Arterioscler Thromb Vasc Biol* 1998;18:432–440.
26. Theoharides TC. The mast cell: a neuroimmunoendocrine master player. *Int J Tissue React* 1996;18:1–21.
27. Stefanadis C, Diamantopoulos L, Vlachopoulos C, Tsiamis E, Dernellis J, Toutouzas K, Stefanadi E, Toutouzas P. Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo: a new method of detection by application of a special thermography catheter. *Circulation* 1999;99:1965–1971.
28. Guazzi MD, Bussotti M, Grancini L, DeCesare N, Guazzi M, Pera IL, Loaldi A. Evidence of multifocal activity of coronary disease in patients with acute myocardial infarction. *Circulation* 1997;96:1145–1151.