Elevated Circulating Levels of C-C Chemokines in Patients With Congestive Heart Failure

Pål Aukrust, MD, PhD; Thor Ueland, SIB; Fredrik Müller, MD, PhD; Arne K. Andreassen, MD; Ingvild Nordøy, MD; Halfdan Aas, MD, PhD; John Kjekshus, MD, PhD; Svein Simonsen, MD, PhD; Stig S. Frøland, MD, PhD; Lars Gullestad, MD, PhD

Background—Immunologic and inflammatory responses appear to play a pathogenic role in the development of congestive heart failure (CHF). Activation and migration of leukocytes to areas of inflammation are important factors in these immunologic responses. Because the C-C chemokines are potent chemoattractants of monocytes and lymphocytes and can modulate other functions of these cells (eg, generation of reactive oxygen species), we measured circulating levels of three C-C chemokines in CHF.

Methods and Results—Levels of macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and RANTES (regulated on activation normally T-cell expressed and secreted) were measured by enzyme immunoassays in 44 patients with CHF and 21 healthy control subjects. CHF patients had significantly elevated levels of all chemokines with the highest levels in New York Heart Association class IV, and MCP-1 and MIP-1α levels were significantly inversely correlated with left ventricular ejection fraction. Elevated C-C chemokine levels were found independent of the cause of the heart failure, but MCP-1 levels were particularly raised in patients with coronary artery disease. Studies on cells isolated from peripheral blood suggested that platelets, CD3+ lymphocytes, and in particular, monocytes, might contribute to the elevated C-C chemokine levels in CHF. The increased MCP-1 levels in CHF were correlated with increased monocyte activity reflected in an enhancing effect of serum from CHF patients on O2− generation in monocytes, which was inhibited by neutralizing antibodies against MCP-1.

Conclusions—This first demonstration of increased circulating levels of C-C chemokines in CHF with particularly high levels in patients with severe disease may represent previously unrecognized pathogenic factors in CHF. (Circulation. 1998;97:1136-1143.)

Key Words: heart failure • coronary disease • chemokines • free radicals • monocytes

Growing evidence suggests that immunologic and inflammatory responses may play a pathogenic role in the development of CHF. For example, recent observations suggest that proinflammatory cytokines (eg, TNF-α and IL-1) are capable of modulating cardiovascular functions by a variety of mechanisms.1 Activation of leukocytes and migration of these cells from the circulation to areas of myocardial inflammation appear to be an important factor in the immunologic responses in CHF.2,3 This leukocyte activation includes granulocytes and T-lymphocytes as well as monocytes. In fact, the activation of monocytes with infiltration into the vessel wall is an early and crucial event in the development of atherosclerosis.4 Monocyte/macrophage activation has also been implicated in the development of acute coronary events,5 and interactions between activated monocytes and human myocardium have been found in CHF independent of the cause of heart failure.5 Also, it has been suggested that activated monocytes and macrophages are important cellular sources for the increased levels of circulating proinflammatory cytokines (eg, IL-1 and TNF-α) found in CHF patients.6,7 These findings may suggest that an adaptive function of monocytes/macrophages may change into a maladaptive and contribute to the progression of CHF.

Chemokines are a family of small molecular mass proteins (8 to 16 kd), which are classified in subfamilies on the basis of their conservation of a four-cysteine motif and of their ability to cause the directed migration of leukocytes in vitro.8 The C-C chemokines are potent chemoattractants of monocytes but may also modulate other functions of this cell population such as generation of ROS and cytokine production.8,9 Thus in view of existing knowledge on the participation of monocytes and proinflammatory cytokines in the pathogenesis of CHF, it is tempting to hypothesize that these C-C chemokines may play a role in the recruitment and
activation of monocytes/macrophages in this disease. There are some in vitro data suggesting that MCP-1 may be involved in the pathogenesis of atherosclerosis. However, to our knowledge, no in vivo data exist on C-C chemokine levels in CHF. In the present study we attempted to study the possible role of C-C chemokines in CHF by different experimental approaches.

**Methods**

**Patients and Control Subjects**

Forty-four patients (35 men and 9 women; 24 to 72 years; mean, 53 years) with chronic symptomatic heart failure, defined as dyspnea or fatigue at rest or on exertion for more than 3 months, were studied (Table 1). The severity of the CHF ranged from New York Heart Association functional class II to IV (Table 1). Their clinical and hemodynamic situations were stable, with no change in medication the last month. Standard medical treatment consisted of ACE inhibitors (80%), diuretics (86%), and digitalis (61%). Most of the patients (n=30) were evaluated by standard right- and left-sided cardiac catheterization. All patients had serum creatinine levels 5 0.5 mg/dL, and renal function was normal in all patients.

**Blood Sampling Protocol**

For serum sampling, blood was drawn into pyrogen-free blood collection tubes without any history of cardiac vascular disease were not included. Control subjects were 21 healthy men and 5 women; 25 to 69 years; mean, 52 years) without any history of cardiac disease or any family history of CAD.

**TABLE 1. Clinical Characteristics of 44 Patients With Congestive Heart Failure**

| Age, y | 53±10 |
| Sex (male/female) | 35/9 |
| NYHA functional class (II/III/IV) | 11/18/15 |
| Cause of heart failure (NYHA class II/III/IV) | n=19/3/10/6 |
| Coronary artery disease | n=18/3/10/6 |
| Idiopathic dilated cardiomyopathy | n=18/6/5 |
| Other* | n=6/0/2/4 |
| Duration of heart failure, y | 4.0±3.6 |
| Left ventricular ejection fraction, %† | 38±18 |
| Pulmonary capillary wedge pressure, mm Hg† | 17±9 |
| Cardiac index, L/min/m²† | 2.2±0.5 |

Data are given as mean±SD.

*Four patients had valvular and two with congenital heart disease.†These hemodynamic parameters were available in 30 of the CHF patients.

**Release of C-C Chemokines From CD3+ Lymphocytes and Monocytes**

CD3+ lymphocytes (10⁶ cells/mL; 200 μL/well) and monocytes (3×10⁶ cells/mL; 200 μL/well) were incubated in flat-bottomed, 96-well microtiter trays (Costar) in medium alone (RPMI 1640 with 2 mmol/L L-glutamine and 25 mmol/L HEPES buffer (mAb) (final concentration, 1.2 ng/mL; clone SpvT b; kindly provided by Bjorn S. Skålehegg, Institute of Medical Biochemistry, University of Oslo, Norway) in combination with anti-CD28

**Isolation of Cells**

Peripheral blood mononuclear cells (PBMC) were obtained from heparinized blood by Isopaque-Ficoll (Lymphoprep, Nycomed Pharma AS) gradient centrifugation within 45 minutes, and further isolation of monocytes was performed by plastic adherence as previously described. For negative selection of CD3+ lymphocytes (T-lymphocytes) by monodisperse immunomagnetic beads, PBMC suspended in phosphate-buffered saline with 0.3% bovine serum albumin (Calbiochem) were mixed with beads coated with antibodies to CD14 (Dynabeads M-450 CD14, Dynal), CD19 (Dynabeads M-459 Pan B, Dynal), and CD56 (clone Bi59, Pharmingen; bound to beads precoated with rat anti-mouse IgG, Dynal) in a cell-to-bead ratio of 1:10 and placed on a rocking platform for 45 minutes. Rosetting cells were removed by application of a magnet (Dynal), and the negative selected T-lymphocytes consisted of >90% CD3+ lymphocytes, as determined by flow cytometry. Endotoxin levels were tested in all media, buffers, and stimulant preparations used in the study and were <10 pg/mL (limulus amoebocyte lysate test).

**Superoxide Anion (O₂⁻) Assay**

The isolated monocytes (3×10⁶/mL; 200 μL/well) were cultured in 96-well trays (Costar) in RPMI 1640 with L-glutamine (Gibco) for 20 hours with 20% of pooled serum from patients or healthy control subjects. For processing of pooled serum, 200 μL of serum from each patient (or control subject) was mixed immediately after thawing, and within 30 minutes the mixed serum solutions were added to monocyte culture at the start of the culture period. In some experiments, neutralizing polyclonal antibodies against MCP-1 (goat anti-human MCP-1; final concentration, 50 μg/mL; R&D Systems), and RANTES (goat anti-human RANTES; final concentration, 50 μg/mL; R&D Systems) or control goat IgG (final concentration, 50 μg/mL; Sigma, St Louis, Mo) were also added to cell cultures. After 20 hours in culture, the generation of O₂⁻ from adherent monocytes was measured by the superoxide dismutase–inhibitable reduction of cytochrome c. Briefly, monocytes were washed twice in prewarmed Hanks’ balanced salt solution (HBSS) without phenol red (BioWhittaker). Thereafter, 100 μL of cytochrome c from horse heart (final concentration, 2 mg/mL; Sigma) in phenol red-free HBSS, with or without stimulants [(phorbol myristate acetate, PMA; final concentration, 100 ng/mL; Sigma) and (unopsonized zymosan; final concentration, 250 μg/mL; Sigma)], was added to each well. At various time points the optical density (OD) was read at 550 nm in a Multiskan Multisoft photometer (Labsystems). Reduction of cytochrome c in the presence of superoxide dismutase (SOD; final concentration, 300 U/mL; Sigma) was subtracted from the values without SOD. The OD differences between comparable wells with or without SOD were converted to the equivalent O₂⁻ release by using the molecular extinction coefficient for cytochrome c. The O₂⁻ production is expressed as nmol/60 minutes per 10⁶ monocytes.
mAb [final concentration, 50 ng/mL; clone 15E8 (402); CLB, Amsterdam, Netherlands]. The cell surface markers were cross-linked with monodispersed immunomagnetic beads coated with sheep anti-mouse IgG (Dynal) at a cell-to-bead ratio of 1:1. Monocytes were stimulated with lipopolysaccharide (LPS) from Escherichia coli O26:B6 (final concentration, 10 ng/mL, Sigma). After culturing for 72 hours, cell-free supernatants were harvested and stored at $-80^\circ$C until analysis.

Release of C-C Chemokines From Platelets in Platelet-Rich Plasma
Preparation and stimulation of platelet-rich plasma (PRP) was performed as previously described. Briefly, a volume of 475 $\mu$L PRP containing $<0.02\times10^9$ leukocytes for all patients and control subjects was incubated by gentle tilting for 30 minutes at room temperature after addition of 25 $\mu$L of the thrombin receptor agonist peptide SFLLRN (stimulated sample) or tris-buffered saline (TS) only (unstimulated sample). The final concentration of SFLLRN was 100 $\mu$mol/L. At baseline and after 30 minutes, equal volumes of PRP were centrifuged at 11,000 $g$ and 4°C for 10 minutes, and platelet-free supernatants were stored at $-80^\circ$C until analysis. The increase in C-C chemokine levels (ng per $10^8$ platelets) in supernatants from unstimulated and stimulated platelets is expressed as concentration in supernatant at the end of the experiment minus concentration in supernatant at baseline.

Enzyme Immunoassays
Levels of MCP-1, MIP-1$\alpha$, and RANTES in plasma, serum (RANTES), and cell culture supernatants were measured by enzyme immunoassays (R&D Systems) according to the manufacturers’ descriptions. At our laboratory, the intra-assay and interassay coefficients of variation were <9% for all assays, the recovery of exogenously added recombinant RANTES from serum was 96%, and the recovery of exogenously added MCP-1 and MIP-1$\alpha$ from EDTA plasma was 96% and 92%, respectively. The detection limit was 8, 10, and 30 pg/mL for MCP-1, MIP-1$\alpha$, and RANTES, respectively.

Measurement of Neopterin Levels
Plasma levels of neopterin were determined by radioimmunoassay (IMMUTest Neopterin, Henning Berlin GMBH), following the manufacturer’s recommendations.

Statistical Analysis
For comparison of two groups of individuals, the Mann-Whitney U test (two-tailed) was used. When more than two groups were compared, the Kruskal-Wallis test was used. If a significant difference was found, Fisher’s least significant difference was computed on the ranks to determine the differences between each pair of groups. Coefficients of correlation ($r$) were calculated by the Spearman rank test. Data are given as medians and 25th to 75th percentiles if not otherwise stated. Probability values are two-sided and considered significant when <.05.

Results
Circulating Levels of C-C Chemokines in Patients With CHF
Patients with CHF had significantly elevated levels of all three C-C chemokines compared with healthy control subjects [MCP-1: 202.1 (159.3 to 231.8) pg/mL versus 120.5 (78.6 to 134.0) pg/mL, $P<.001$; MIP-1$\alpha$: 24.3 (20.2 to 29.0) pg/mL versus 17.8 (15.8 to 19.7) pg/mL, $P<.001$; RANTES: 22.2 (13.8 to 41.5) ng/mL versus 11.2 (10.2 to 13.3) ng/mL, $P<.001$; CHF patients and control subjects, respectively]. The highest levels were found in NYHA class IV for all three C-C chemokines (Fig 1). However, although there was a gradual increase in plasma levels of MIP-1$\alpha$ and in particular MCP-1 along with increasing NYHA class, serum levels of RANTES were significantly elevated only in NYHA class IV (Fig 1).
To further examine the relation between the degree of heart failure and circulating levels of C-C chemokines, levels of MCP-1, MIP-1α, and RANTES were correlated with hemodynamic parameters in the patient group. As can be seen in Fig 2, we found a significantly inverse correlation between both MCP-1 and MIP-1α levels, but not RANTES levels and left ventricular ejection fraction. No significant correlations were found between circulating levels of these three C-C chemokines and either pulmonary capillary wedge pressure or cardiac index (data not shown).

We next examined whether the C-C chemokine levels were related to the cause of cardiac disease. To avoid the influence of the high percentage of patients with idiopathic dilated cardiomyopathy (IDCM) in NYHA class II (Table 1), only patients with severe CHF (NYHA class III and IV) were studied. We found significantly elevated levels of all three C-C chemokines irrespective of the cause of the CHF. However, although the CAD group had the lowest percentage of patients in NYHA class IV (Table 1), plasma levels of MCP-1 were significantly higher in CAD patients compared with the two other groups [CAD patients: 240.9 (210.5 to 372.7) pg/mL, IDCM patients: 205.1 (156.8 to 232.0) pg/mL, other patients: 199.2 (180.8 to 230.6) pg/mL; *P< .05, CAD patients versus both IDCM patients and other patients]. A similar pattern was found when NYHA class III and class IV was analyzed separately. No such differences between the three groups were found for RANTES and MIP-1α levels (data not shown).

Thus it appears that levels of MCP-1, MIP-1α, and RANTES are significantly elevated in patients with CHF, with particularly high levels in patients with the most severe heart failure evaluated both clinically (NYHA group IV) and hemodynamically (low ejection fraction). This increase is found independent of the cause of the heart failure. However, MCP-1 levels appear to be particularly elevated in patients with CAD.

Release of C-C Chemokines From T-Lymphocytes, Monocytes, and Platelets in Peripheral Blood

To possibly define the cellular sources of the enhanced C-C chemokine levels in CHF, spontaneous and stimulated release of MCP-1, MIP-1α, and RANTES from CD31 lymphocytes (T-lymphocytes), monocytes, and platelets were measured in 5 CHF patients, all in NYHA class III-IV, and in 6 healthy control subjects. Platelets were activated by the thrombin receptor agonist peptide SFLLRN, and monocytes and CD3+ lymphocytes were stimulated with LPS and anti-CD3/anti-CD28 mAbs, respectively. Both stimuli are known to be potent inducers of C-C chemokines in these cells.5,14 As can be seen in Table 2, several differences between CHF patients and control subjects were revealed. First, platelets from CHF patients released sig-
TABLE 2. Release of C-C Chemokines From Platelets, Monocytes, and CD3+ Lymphocytes in 5 Patients With Severe CHF (NYHA Class III-IV) and 6 Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Platelet-Rich Plasma*</th>
<th>Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstimulated</td>
<td>SFLLRN-Stimulated</td>
</tr>
<tr>
<td></td>
<td>Control Subjects</td>
<td>CHF</td>
</tr>
<tr>
<td>RANTES, ng/mL</td>
<td>0.8</td>
<td>3.3</td>
</tr>
<tr>
<td>(0.7–1.0)</td>
<td>(2.4–4.7)‡</td>
<td>(21.3–57.9)</td>
</tr>
<tr>
<td>MIP-1α, ng/ml‡</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>MCP-1, ng/mL‡</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>(12.5–21.6)</td>
<td>(21.8–31.2)†</td>
<td>(34.7–95.6)</td>
</tr>
</tbody>
</table>

*Data are given as medians and ranges.

‡No increase in MIP-1α and MCP-1 levels was found in unstimulated and SFLLRN-stimulated platelets in PRP in neither patients or control subjects.

Discussion

There are several reports on elevated circulating levels of proinflammatory cytokines in patients with CHF, that is, IL-1, IL-6, and TNF-α. However, this is to our knowledge the first report of raised levels of C-C chemokines in these patients, with particularly high concentrations in those with the most severe CHF. The C-C chemokine levels were increased independent of the cause of heart failure, but particularly high MCP-1 levels were found in patients with CAD. Furthermore, in vitro experiments suggest that both platelets, CD3+ lymphocytes, and in particular monocytes, may contribute to the elevated circulating levels of C-C chemokines in CHF.
elevated C-C chemokine levels in CHF. Finally, an enhancing effect of serum from CHF patients on spontaneous $O_2^-$ generation in monocytes was inhibited by the addition of neutralizing antibodies against MCP-1. These findings suggest that enhanced C-C chemokine levels may represent a previously unrecognized pathogenic factor in CHF.

Enhanced levels of C-C chemokines have been found in a variety of acute (eg, bacterial sepsis, 17 adult respiratory distress syndrome, 18 and allograft rejection 19) and chronic (eg, human immunodeficiency virus infection, 20 parasitic infections, 21 rheumatoid arthritis, 22 pulmonary sarcoidosis, 23 and allergic disorders 24) inflammatory and immune-mediated diseases. However, although the raised circulating levels of C-C chemokines are not specific for CHF, we believe that our findings support the notion that immunologic and inflammatory processes are important features of CHF.

MCP-1, MIP-1α, and RANTES are produced by a variety of leukocytes and RANTES also by platelets, whereas MCP-1 is also produced by endothelial cells and fibroblasts. 8,13 In the present study we found that platelets, CD3+ lymphocytes, and in particular monocytes from CHF patients, released higher amounts of these C-C chemokines than cells from healthy control subjects, and may therefore contribute to the elevated C-C chemokine levels in CHF. The increased in vitro release of RANTES from unstimulated and SFLLRN-stimulated platelets associated with enhanced release of MCP-1 from unstimulated and LPS-stimulated monocytes is of particular interest. Activated platelets have been found to stimulate MCP-1 production in monocytes through enhanced RANTES secretion and direct platelet-monocyte contact mediated by P-selectin expression on the platelet surface.25 Such a mechanism for enhanced MCP-1 expression in leukocytes has recently been found to be operative in patients with acute myocardial infarction, 26 and it is conceivable that such a platelet-monocyte interaction also may contribute to the enhanced C-C chemokine levels in CHF.

There are at present no reports in humans or in animal models of production of C-C chemokines in cardiomyocytes. However, although we found increased release of C-C chemokines from platelets, monocytes, and CD3+ lymphocytes

<table>
<thead>
<tr>
<th>CD3+ Lymphocytes</th>
<th>Control Subjects</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD3/CD28-Stimulated</td>
<td>25.5</td>
<td>54.7</td>
</tr>
<tr>
<td></td>
<td>(18.1–37.8)</td>
<td>(45.7–64.5)†</td>
</tr>
<tr>
<td></td>
<td>85.9</td>
<td>103.2</td>
</tr>
<tr>
<td></td>
<td>(53.4–100.4)</td>
<td>(82.5–117.4)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>(0.2–1.3)</td>
<td>(0.8–3.1)</td>
</tr>
</tbody>
</table>

Figure 4. The effect of serum from CHF patients on the generation of $O_2^-$ in monocytes. Monocytes from 6 healthy blood donors were evaluated for spontaneous (A) and zymosan- (B) and PMA- (C) stimulated $O_2^-$ generation after culturing for 20 hours in medium supplemented with either 20% pooled serum from 7 CHF patients with markedly elevated MCP-1 levels (>300 pg/mL; median, 450 pg/mL), 20% pooled serum from 7 patients with moderately elevated MCP-1 levels (150 to 300 pg/mL; median, 215 pg/mL), or 20% pooled serum from 7 healthy blood donors (<150 pg/mL; median, 105 pg/mL). **$P<.01$ vs serum from healthy control subjects, *$P<.05$ vs serum from healthy control subjects. Data are given as medians and ranges.

TABLE 2. Continued

<table>
<thead>
<tr>
<th>CD3+ Lymphocytes</th>
<th>Control Subjects</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD3/CD28-Stimulated</td>
<td>25.5</td>
<td>54.7</td>
</tr>
<tr>
<td></td>
<td>(18.1–37.8)</td>
<td>(45.7–64.5)†</td>
</tr>
<tr>
<td></td>
<td>85.9</td>
<td>103.2</td>
</tr>
<tr>
<td></td>
<td>(53.4–100.4)</td>
<td>(82.5–117.4)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>(0.2–1.3)</td>
<td>(0.8–3.1)</td>
</tr>
</tbody>
</table>
isolated from peripheral blood, it may well be that the failing heart might directly contribute to the elevated levels of these chemokines. Interestingly, enhanced levels of MCP-1 have been found in cardiac lymph and in the endothelium of small veins from ischemic canine myocardium. Furthermore, a recent study demonstrated elevated levels of RANTES and MIP-1α in situ in cardiac allografts in humans. These findings suggest that the failing myocardium has the potential to secrete C-C chemokines, at least by infiltrating platelets and leukocytes. Future studies are needed to clarify whether endothelial cells in the myocardium or cardiomyocytes may also be a source of chemokines in CHF.

Whatever the cellular sources, the enhanced levels of C-C chemokines may both indirectly and directly have important pathophysiological consequences in patients with CHF. MIP-1α, RANTES, and MCP-1 have chemotactic activity for both monocytes and lymphocytes, and in particular MCP-1 has been postulated to be a major signal for the accumulation of mononuclear leukocytes in diseases. There are several reports suggesting that infiltration of lymphocytes and monocytes into the failing myocardium by various mechanisms may lead to reversible and irreversible damage of the cardiac muscle. By playing a crucial role in the recruitment of these cells into sites of inflammation, C-C chemokines may thus indirectly play an important role in the pathogenesis of cardiac dysfunction. The possible importance of C-C chemokines for the induction of cardiac damage was recently illustrated by Cook et al, finding that homozygous MIP-1α mutant (−/−) mice were resistant to Coxsackie virus-induced myocarditis in contrast to wild-type (+/+ mice).

C-C chemokines may also more directly induce dysfunction of the cardiac muscle. In the present study we found that the raised MCP-1 levels in serum from CHF patients had enhancing effects on spontaneous ROS generation in monocytes, and if this enhancement also occurs in vivo in myocardial tissue, it may be involved in the increased apoptosis of cardiomyocytes found in patients with severe heart failure. The lack of effect of neutralizing antibodies against MCP-1 on the enhancement of CHF serum on PMA- and zymosan-stimulated O2− generation most probably reflects that other proinflammatory cytokines, known to be elevated in CHF, may prime monocytes for enhanced ROS generation on further stimulation. Whatever the reason, this increased ROS generation in monocytes may further enhance the synthesis of MCP-1 in these cells through an autocrine mechanism, possibly representing a vicious circle operative in CHF.

On the basis of the observations described above, it is tempting to hypothesize that enhanced C-C chemokine levels, possibly in combination with other proinflammatory cytokines, may be an important factor in mediating the infiltration and activation of mononuclear leukocytes into the myocardium in patients with CHF, thereby playing an important pathogenic role in the development of cardiac failure.

In this study we found that CAD patients had significantly higher MCP-1 levels compared with other patients with severe
CHF. Cellular components of the normal arterial wall can secrete MCP-1 in response to oxidized LDL and increased MCP-1 secretion from these cells, leading to infiltration of monocytes into the arterial wall, has been suggested to be a crucial step in the development of atherosclerosis. In advanced atherosclerotic lesions the MCP-1 secretion may be particularly enhanced, possibly because of increased expression of the activated transcription factor nuclear factor-κB. Although several other cytokines and chemoattractant signals may be involved in the pathogenesis of atherosclerosis, our study supports an association between CAD and enhanced MCP-1 levels.

In conclusion, the results of this study, demonstrating for the first time elevated C-C chemokine levels in CHF patients, significantly correlated with the severity of symptoms and with the degree of left ventricular dysfunction, suggest that the raised C-C chemokine levels may not only be a “new” parameter of enhanced immune activation in CHF but may also reflect important pathogenic mechanisms in this disease. These results should warrant further studies investigating the possible pathogenic role of C-C chemokines in the development of CHF.

Acknowledgments

This work was supported by the Norwegian Council of Cardiovascular Disease, the Norwegian Cancer Society, the Research Council of Norway, Anders Jahre’s Foundation, and Medinnova Foundation. We thank Bodil Lunden and Lisbeth Wikeby for excellent technical assistance.

References

Elevated Circulating Levels of C-C Chemokines in Patients With Congestive Heart Failure
Pål Aukrust, Thor Ueland, Fredrik Müller, Arne K. Andreassen, Ingvild Nordøy, Halfdan Aas, John Kjekshus, Svein Simonsen, Stig S. Frøland and Lars Gullestad

_Circulation_. 1998;97:1136-1143
doi: 10.1161/01.CIR.97.12.1136

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/12/1136

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/