Upregulation of cell adhesion molecules and the presence of low grade inflammation in human chronic heart failure

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Background In the present study, the hypothesis was tested that cell adhesion molecules are expressed in failing human hearts and that a chronic inflammatory process contributes to chronic degeneration known to occur in cardiac incompetence. The cell adhesion molecules: ICAM-1, VCAM-1, PECAM-1, and E-selectin were studied, in addition to cellular markers of inflammation.

Methods and results Tissue was obtained at transplantation from patients with either myocarditis, chronic ischemic heart disease, or dilated cardiomyopathy. Controls were taken from patients with normal ventricles. Cell adhesion molecules were qualitatively evaluated and counted using specific antibodies and confocal microscopy. Additionally, semiquantitative evaluation of the presence of the CD3 antigen (T-lymphocytes), CD68 (macrophages), CD11a/CD18 (ICAM-1 receptor) and human tumour necrosis factor-α were used as indicators of chronic inflammation. PECAM-1 stained all endothelial cells but ICAM-1 was only present in 80% of all capillaries in control tissue. The ratio ICAM-1/PECAM-1 was significantly enhanced in all groups of diseased hearts. Myocytes in myocarditic hearts expressed ICAM-ICAM. CD3 positive lymphocytes, CD68 positive macrophages and CD11a/CD18 positive cells were more abundantly present than in control. Macrophages expressing tumour necrosis factor-α were found in failing myocardium but not in control tissue.

Conclusion Independent of the cause of heart failure, chronic low grade inflammation is present in failing human myocardium. This may significantly contribute to the structural deterioration that is the basis of reduced cardiac function in congestive heart failure.

Key Words: Cell adhesion molecules, heart failure, inflammation.

Introduction

Congestive heart failure is the consequence of different heart diseases and is a significant cause of cardiac death. Effective therapy has been hampered by incomplete understanding of the pathophysiological mechanism leading to this situation. In recent studies, our group reported that degeneration of the contractile and cytoskeletal apparatus in myocytes is one of the components leading to functional deterioration and final failure of human hearts[1,2]. In hearts from patients with dilated cardiomyopathy it was also noted that CD3 positive T-lymphocytes were present, indicating low grade chronic inflammation. It seemed appropriate, therefore, to study the expression of vascular adhesion molecules and the possibility that an inflammatory reaction exists that could contribute to the structural and functional deterioration observed in failing human hearts.

Expression of cell adhesion molecules determines the interaction between endothelial cells and various types of leukocytes from the circulating blood (reviewed in[3,4]) and cell adhesion molecules are therefore implicated in many cardiovascular diseases such as allograft rejection, myocarditis, atherosclerosis, ischaemia-reperfusion injury and vasculitis[5-8]. Three main classes of molecules have been identified[9]. The selectins comprise the endothelial leukocyte cell adhesion molecule E-selectin and P-selectin, present on endothelial cells and platelets, and L-selectin present on leukocytes[9]. The selectins are responsible for the induction of rolling and sticking of leukocytes to the endothelial cells. The immunoglobulin superfamily consists of the platelet endothelial cell adhesion molecule-1 (PECAM-1), the intercellular cell adhesion molecule-1 (ICAM-1), and...
the vascular cell adhesion molecule-1 (VCAM-1)\textsuperscript{10,11}. Adhesion molecules interact with specific integrins on different types of leukocytes\textsuperscript{11,12} and establish firm attachment to endothelial cells. Among these, the LFA-1 integrin (CD11a/CD18) and MAC-1 (CD11b/CD18) are the specific ligands for ICAM-1\textsuperscript{13}. These adhesion molecule-integrin interactions make possible the migration of leukocytes through the endothelial layer into regions of inflammation.

Abundant ICAM-1 expression has been observed after interleukin-1 or tumour necrosis factor-\alpha stimulation of cultured endothelial cells. Persistent ICAM-1 expression is characteristic of chronic inflammatory disorders\textsuperscript{13,15} but expression of E-selectin and VCAM-1 indicates damage to the endothelium and acute inflammation\textsuperscript{13,14}.

PECAM-1 is constitutively expressed\textsuperscript{15} and remains unchanged after stimulation with cytokines. Therefore, it can be used for the identification of vascular endothelial cells and for the determination of the total number of vessels in tissue.

The occurrence of adhesion molecules, especially ICAM-1, has rarely been studied in biopsy tissue with immunohistochemistry\textsuperscript{16,17}. Morphological investigations offer the advantage that the type of cells expressing an adhesion molecule can be identified and the expression quantified with regard to the total number of vessels. The present study was designed to evaluate the presence of E-selectin, VCAM-1, PECAM-1, and ICAM-1 in human hearts failing because of acute myocarditis, dilated cardiomyopathy or ischaemic heart disease. The ICAM-1 ligand CD11a/CD18, CD3 for T-lymphocytes and CD68 as a marker for macrophages were also studied and confirmed the presence of chronic inflammation. Tumour necrosis factor-\alpha was found in myocarditis and eosin in order to identify blocks with transverse arrangement of myofibres. Thereafter, serial cryosections 4 \textmu m thick were prepared from all blocks and placed on gelatine-coated slides. Cryosections as well as cells from the cell culture were fixed in 4\% freshly prepared formaldehyde in phosphate buffered saline. After fixation, the cells were permeabilized in 0.05\% Triton \times 100 in phosphate buffered saline for 10 min, blocked in 0.1 M glycine in phosphate buffered saline for 10 min, then in 5\% bovine serum albumin + 0.2\% gelatine for 10 min, and transferred to the reaction buffer: 0.01\% Triton \times 100+0.1\% carbosilated bovine serum albumine (AURION, Netherlands) in phosphate buffered saline, pH 7.6.

Materials and methods

Patients

Twenty-four hearts from patients in end-stage heart failure (18 men, 6 women, 44 ± 11 years, ejection fraction <20\%) were studied. This group included six patients with myocarditis, six with chronic ischaemic heart disease and 12 with dilated cardiomyopathy.

The clinical diagnosis was established using routine cardiological procedures including echocardiography, ventriculography, and coronary angiography, and in the case of myocarditis by histopathological evaluation of catheter biopsies. All patients underwent transplantation surgery because of intractable heart failure and the tissues were obtained on this occasion. From each heart, 10 random samples were obtained from the anterior, lateral and posterior left ventricular wall.

Control tissues were left ventricular biopsies removed intra-operatively from six patients (5 men, one woman, mean age 35 ± 7 years) undergoing mitral valve replacement, without clinical evidence of abnormal left ventricular function.

Informed consent was obtained from all patients.

Cell cultures

Human umbilical vein endothelial cells from passage 0–2 seeded on fibronectin coated culture chamber slides (Nunc, Naperville, Illinois, U.S.A.) were used as positive control. For stimulation experiments, confluent monolayers were washed twice with HEPES and overlaid with Waymouth's culture medium supplemented with 0.2\% fetal calf serum containing interleukin-1/\beta (Bachem, Bubendorf, Switzerland) at a concentration of 2 ng ml\textsuperscript{-1} (ED50 = 0.1 ng ml\textsuperscript{-1}) for 1–24 h. Cells were examined before and 8 h after stimulation with interleukin-1/\beta to evaluate the expression of cell adhesion molecules.

Preparation and fixation

All tissue samples were frozen in liquid nitrogen, stored at −80°C and later embedded in OCT compound (Tissue Teck; Miles Inc., Elkhart, Indiana, U.S.A.). All blocks per patient were cut and stained with haematoxylin and eosin in order to identify blocks with transverse arrangement of myofibres. Thereafter, serial cryosections 4 \textmu m thick were prepared from all blocks and placed on gelatine-coated slides. Cryosections as well as cells from the cell culture were fixed in 4\% freshly prepared formaldehyde in phosphate buffered saline. After fixation, the cells were permeabilized in 0.05\% Triton \times 100 in phosphate buffered saline for 10 min, blocked in 0.1 M glycine in phosphate buffered saline for 10 min, then in 5\% bovine serum albumin + 0.2\% gelatine for 10 min, and transferred to the reaction buffer: 0.01\% Triton \times 100+0.1\% carbosilated bovine serum albumine (AURION, Netherlands) in phosphate buffered saline, pH 7.6.

Immunohistochemistry

After rinsing with phosphate buffered saline, cryosections as well as cells were incubated for 1 h with monoclonal primary antibodies against either ICAM-1 (clone 15-2, Biotrend, Köln, Germany), PECAM-1 (clone JC-70A, Dakopatts, Hamburg, Germany), VCAM-1 (clone BBIG-V1, Biermann, Bad Nauheim, Germany), E-selectin (clone BBIG-E4, Biermann, Bad Nauheim, Germany), macrophages and T-lymphocytes (CD68, CD3 Dakopatts, Hamburg, Germany) or LFA-1 (CD11a/CD18, clone BAQ30, VMDR, Pullman,
U.S.A) in a moist chamber at room temperature. Subsequently, the sections were washed three times (3 min each) in phosphate buffered saline. Incubation in biotinylated goat antimouse immunoglobulin G, at a dilution of 1:100 (Dianova, Hamburg, Germany), was followed by several rinses with phosphate buffered saline and afterwards the sections were incubated for 30 min with streptavidin fluorescein isothiocyanate (FITC, Amersham, U.K.) or streptavidin-Cy2 at a dilution of 1:50. Rinsing with phosphate buffered saline was followed by counterstaining of the nuclei with 0.002% propidium iodide or 7-AAD (Molecular Probes, Eugene, U.S.A.) and mounting of the tissue sections with Mowiol (Hoechst, Frankfurt/M., Germany).

Capillaries were also affinity-stained with the lectin from Ulex Europeus (FITC-labelled lectin, Sigma, München, Germany) at a dilution of 1:4.

**Immunostaining for tumour necrosis factor-α**

Cryostat sections of 4 μm thickness were fixed in acetone at −20 °C for 10 min. After rinsing with phosphate buffered saline, sections were incubated overnight at 4 °C with a murine monoclonal antibody to tumour necrosis factor-α (Miles, Elkhart, IN, U.S.A.; diluted 1:10). FITC-coupled goat anti-mouse IgG diluted 1:200 (Dianova, Hamburg, Germany) was then applied at room temperature for 60 min. As nuclear stain, 0.002% propidium iodide was used and the sections were mounted with Mowiol (Hoechst, Frankfurt/M, Germany).

All sections were viewed with a Leica confocal microscope/Leitz Aristoplan LM microscope (Bensheim, Germany) and documentation was carried out on professional film, Kodak Ektachrome 100 HC for colour slides.

**Electron microscopy**

The reaction for ICAM-1 was carried out as described above as a pre-embedding procedure. The detection system comprised ultra-small (US-grade 0.8 nm) gold-conjugated goat anti-mouse secondary antibodies (AURION, Netherlands) followed by enhancement in silver lactate to about 20 nm. After post-fixation in OsO₄, the tissue was embedded in Epon and semi-thin (1 μm) sections were stained with toluidin blue and viewed through a LEICA DM microscope. Ultra-thin sections were stained with uranyl acetate and lead citrate and viewed and photographically recorded in a Philips CM 10 electron microscope.

Controls for the specificity of the immunohistochemical reactions were carried out for all procedures, following the same staining protocol as described above. However, the first antibody was replaced by the reaction buffer. Human umbilical vein endothelial cells were used as positive control.

**Results**

Fibrotic tissue was present in varying amounts in all patients and usually contained only a few fibroblasts, endothelial cells and macrophages. Mononuclear cellular infiltrates in patients with myocarditis contained abundant capillaries and inflammatory cells. Both areas were excluded from the evaluation described here, in order to make a comparison between groups possible.
Figures 1–5 PECAM-1 in human myocardium. (a) All blood vessels are positively labelled in cross section. (b) In the confocal microscope, the longitudinal zigzag course of the capillaries becomes evident (arrows). Figure 2 Control human myocardium. (a) Staining for PECAM-1 shows that all vessels are labelled. (b) Staining for ICAM-1 is not positive in all capillaries. Arrows indicate unstained vessels. Figure 3 Immunogold labelling for ICAM-1 in control myocardium viewed through the light microscope. Specific labelling is brown. Not all vessels are labelled (arrows). Figure 4 Immunogold labelling for ICAM-1 in normal human myocardium: electron microscopy shows that only the luminal side of the vascular endothelium is labelled for ICAM-1. Figure 5 ICAM-1 labelling in failing myocardium shows that all capillaries are positively stained.

In all illustrations, if not mentioned otherwise, the specific fluorescence is green, nuclei are red. The bars are 20 μm in all micrographs except in electron microscopy where it is 2 μm.
Table 1  Quantitative evaluation of PECAM-1 and ICAM-1 labelled blood vessels in human myocardium and ratio ICAM-1/PECAM-1

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n.mm⁻²)</th>
<th>Myocarditis (n.mm⁻²)</th>
<th>Ischaemia (n.mm⁻²)</th>
<th>DCM (n.mm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PECAM-1</td>
<td>1176 ± 179</td>
<td>948 ± 192</td>
<td>1027 ± 85</td>
<td>1418 ± 317</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>930 ± 139</td>
<td>972 ± 187</td>
<td>1037 ± 105</td>
<td>1393 ± 186*</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.82 ± 0.04</td>
<td>1.05 ± 0.09*</td>
<td>1.05 ± 0.10*</td>
<td>0.99 ± 0.16*</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

Mean ± SEM. DCM = dilated cardiomyopathy.

*P<0.05 vs control.

Labelling of human umbilical vein endothelial cells

Labelling of human umbilical vein endothelial cells served as a control procedure and provided results as described previously[18]. PECAM-1 was constitutively expressed in human umbilical vein endothelial cells where it occurred on the entire cell membrane. ICAM-1 was expressed in 30% of all cells and increased to 100% in stimulated cells. E-selectin and VCAM-1 were present in cultured endothelial cells after stimulation with interleukin-1β.

E-selectin and VCAM-1

These adhesion molecules were absent in tissue sections from human hearts.

PECAM-1

In human myocardium, PECAM-1 labelled all endothelial cells (Fig. 1) independent of the size or type (arterial or venous) of the vessel. The number of capillaries could therefore be counted and capillary density calculated as n.mm⁻² (Table 1).

Ulex staining confirmed the results obtained with PECAM-1 (1070 ± 56 mm⁻² with Ulex vs 1077 ± 85 with PECAM-1 antibody, counted from the group with ischaemic hearts).

Capillary density in all groups was not different from control, but patients with myocarditis had a decreased capillary density as compared to patients with dilated cardiomyopathy.

ICAM-1

In control human myocardium, not all blood vessels were positively stained for ICAM-1, as shown by a comparison on serial sections stained for PECAM-1 (Fig. 2). ICAM-1 was labelled only at the luminal side of the blood vessel as evidenced by light (Fig. 3) and electron microscopy (Fig. 4). Some leukocytes were also stained for ICAM-1.

In diseased human myocardium, ICAM-1 was observed in all endothelial cells of blood vessels regardless of size (Fig. 5), but only capillaries were counted (Table 1). It is evident from this table that the number of vessels stained for ICAM-1 was significantly greater in patients with dilated cardiomyopathy as compared to control. It is also evident that the ratio ICAM-1/PECAM-1 is significantly greater in all groups as compared to the control group.

In samples from myocarditis, myocytes bordering the areas of inflammation expressed ICAM-1 (Fig. 6). All other myocytes were found to be negative.

Figures 6-12  ICAM-1 labelled myocytes in tissue with myocarditis viewed with confocal microscopy (a) original and (b) three-dimensional reconstruction. Myocytes are distinctly positive for ICAM-1 (green), background is blue, nuclei are red. Typical positive myocytes are indicated by arrows. Figure 7  Myocardium with dilated cardiomyopathy stained with CD3 antibody. Several T-lymphocytes are present in the interstitial space. Figure 8  CD68 positive macrophages in myocardium with dilated cardiomyopathy. Figure 9  CD68 labelling in non-fibrotic myocardium with ischaemic heart disease, confocal microscopy and three-dimensional reconstruction. Macrophages labelled in green are situated around a blood vessel and in the interstitial space, the background (corresponding to myocytes) is blue, nuclei are red. Figure 10  Myocardium with dilated cardiomyopathy. LFA-1 is labelled with anti-CD11a/CD18. Numerous cells are positive for the ICAM-1 receptor on activated leukocytes. Positive cells are red, endothelial cells are green and nuclei are blue. Figure 11  Staining for tumour necrosis factor-α in dilated cardiomyopathy (a and b) and in myocardium with myocarditis (c). Single cells as in 11(a) or numerous tumour necrosis factor-α positive cells as in 11(b) are evident. In myocardium with a focal inflammatory area the number of tumour necrosis factor-α positive macrophages is elevated (c). Figure 12  Negative control with omission of the first antibody lacks any labelling indicating the specificity of the reactions.

In all illustrations, if not mentioned otherwise, the specific fluorescence is green, nuclei are red. The bars are 20 μm in all micrographs except in electron microscopy where it is 2 μm.

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CD3, CD68, CD11a/CD18 and tumour necrosis factor-α

CD3 positive cells were observed in variable numbers in the extracellular space of all tissues except for the control myocardium. The lymphocytes were situated around blood vessels or they were dispersed throughout the extravascular space (Fig. 7).

Macrophages stained by CD68 were abundant (Figs 8 and 9). These cells were much larger than fibroblasts or lymphocytes and often contained lipofuscin showing the typical yellow autofluorescence. Cells positive for CD11a/CD18 were inhomogeneously distributed throughout the tissue (Fig. 10). They were observed in and around blood vessels and could be identified as leukocytes by double staining in serial sections with the pan-leukocyte marker CD45.

Tumour necrosis factor-α was found in macrophages in the interstitial space in all three groups of patients but it was absent from normal tissue (Fig. 11). The negative control lacked any specific fluorescence (Fig. 12). Table 2 summarizes these findings.

**Table 2** Semiquantitative evaluation of the occurrence of lymphocytes, macrophages and cells positive for CD11a, CD18 and TNF-α

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Myocarditis</th>
<th>Ischaemia</th>
<th>DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>±</td>
<td>++</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>CD11a/CD18</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>CD68</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>TNF-α</td>
<td>−</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

DCM = dilated cardiomyopathy; TNF-α = tumour necrosis factor-α. ± <10 mm²; + 10–20 mm²; ++ >20 mm².

**Western blot**

PECAM-1 and ICAM-1 were present in all samples including control tissue, but the density of the bands differed indicating variations of antigen abundance between patients. Human umbilical vein endothelial cells were used as positive controls and confirmed the specificity of staining obtained in human myocardium (Fig. 13).

**Discussion**

In the present study, we investigated the presence of adhesion molecules and of inflammatory cells in myocardium from human hearts failing because of either dilated cardiomyopathy, acute myocarditis, or ischaemic heart disease. Chronic low grade inflammation indicated by activation of the vascular endothelium and numerous inflammatory cells was found to be present in all three groups of patients.

Human heart capillaries can express VCAM-1 and E-selectin (19–21). VCAM-1 is often suggested as a marker of allograft rejection (20,22), but in controls VCAM-1 is not expressed (17,23). Similarly, E-selectin is neither spontaneously expressed in human heart recipients (24) nor in murine cardiac graft models (23). In human umbilical vein endothelial cells, the expression of...
VCAM-1 and E-selectin after cytokine stimulation is only visible for 2–6 h and declines rapidly thereafter. This observation explains the absence of VCAM-1 and E-selectin and confirms the absence of an acute inflammatory response in failing myocardium.

PECAM-1 was used to determine the total number of capillaries and ICAM-1 was used as an indicator of endothelial cell activation. Immunohistochemistry, the main method employed in this study, allows for the exact localization of the presence of the antigen and the identification of the structure expressing it. This morphological method, however, has limitations with regard to the quantitation of the amount of the antigen present. Therefore, a Western blot was carried out that showed that there is a variation in the abundance of the antigen, e.g. PECAM-1 or ICAM-1. The main finding of this study, however, is that ICAM-1 is expressed in diseased myocardium by more capillaries than in control tissue, and that this type of result can only be obtained using morphological methods.

PECAM-1 is found on the surface of platelets, endothelial cells and cells of myeloid lineage. It either shows homophilic binding to PECAM-1 or it binds to an as yet unknown receptor. PECAM-1 is most probably responsible for the maintenance of the endothelial integrity; it participates in leukocyte migration through the endothelium and is therefore involved in inflammatory processes. In our tissues, all endothelial cells from capillaries, veins and arteries were stained. Since 99-9% of all myocardial vessels are capillaries, it is safe to assume that the values in this study represent capillary density.

Capillary density determined by immunostaining for PECAM-1 was similar to values reported by Yarom et al. using the electron microscope, but lower than those reported by Rakusan. Therefore, several controls were carried out. The specificity of the monoclonal antibodies against the four cell adhesion molecules was confirmed by using human umbilical vein endothelial cells as positive control. In addition, Ulex European lectin and PECAM-1 staining were compared and produced identical numbers of stained vessels in human myocardium. Capillary density was not changed in failing myocardium, as compared to the control group, which confirms data by other groups.

Expression of ICAM-1 on endothelial cells

As a central component of the mechanism of leukocyte-endothelial adhesion, ICAM-1 plays a decisive role in mediating cellular immune and inflammatory responses. ICAM-1 is constitutively expressed in a certain percentage of endothelial cells and it is strongly up-regulated in vitro and in vivo by several cytokines. In studies of vasculitis, inflammatory skin disease and heart rejection, it has been shown that ICAM-1 is a reliable indicator of inflammation because ICAM-1 expression correlated well with the degree of inflammation determined by conventional histology. Therefore, increased ICAM-1 expression is indicative of activation of the endothelium as part of the inflammatory process.

Our results show that 80% of myocardial endothelial cells in control tissue expressed ICAM-1. Tanio et al. found 53% of control blood vessels expressing ICAM-1. Expression of ICAM-1 was, however, increased in all groups of patients and the ratio ICAM-1/PECAM-1 was significantly higher than in control tissue. Marijanoński et al., in a different context, reported the localization of ICAM-1 on all vessels in failing myocardium, and Tsutamoto et al. believes that sICAM plasma levels have prognostic value in patients with congestive heart failure.

In dilated cardiomyopathy, immunological abnormalities and an abnormal increase in the expression of autoantigens has been described. We confirm with this study the presence of an inflammatory reaction in dilated cardiomyopathy. These findings should not, however, lead to the conclusion that inflammation plays a causative role in the pathogenesis of dilated cardiomyopathy because increased ICAM-1 expression may be secondary to the humoral or cytokine changes associated with cardiomyopathy and heart failure.

In myocarditis, in the presence of mononuclear infiltrates of focal inflammation and necrosis, the increased ICAM-1/PECAM-1 ratio in the non-infiltrated myocardium probably reflects the generalized reaction of the endothelium to the release of cytokines in the entire heart.

In patients with chronic ischaemic heart disease, upregulation of the CD11b/CD18 receptor in neutrophils and monocytes was used as an indirect indicator of the presence of ICAM-1 in the endothelium of coronary vessels. Expression of ICAM-1 in arterio-arteriolar coronary vessels in post-transplantation patients may be an indicator of transplant-induced arteriopathies. However, as shown in the present study, the fact that the cardiac microvasculature from patients with chronic ischaemic heart disease exhibits significant ICAM-1 expression is new. In larger vessels, thrombotic events may be influenced by the activation of leukocytes and platelets but in capillaries an inflammatory process prevails.

Expression of ICAM-1 on myocytes: a contribution to cell death?

Myocytes have been described expressing ICAM-1 during fetal development during graft rejection in human heart transplantation, after stimulation with tumour necrosis factor-α in the rat and after ischaemia–reperfusion in the canine heart. ICAM-1 is normally only expressed in a few cell types, but can be induced in inflammatory sites by cytokines, which are known to induce ICAM-1 expression on cardiac myocytes in culture. Seko et al. suggested that natural killer cells locally release cytokines which induce the expression of major histocompatibility complex and ICAM-1 on myocytes and prepare the contact with T-cells. Ban et al. in neonatal rat myocytes in culture exposed to interleukin-1β found monocyte
endothelium and therefore to expression of ICAM-1. The presence of ICAM-1 positive endothelial cells or extracellular matrix by the occurrence of cellular debris.

It is, therefore, believed that the denominator in these different diseases appears to be the degeneration of myocytes and the stimulation of the extracellular matrix by the occurrence of cellular debris. The primary activation of macrophages was probably caused by sequestration of cellular particles from the myocytes undergoing degeneration because of either viral infections, autoimmune processes or oxygen deficiency.

From a cellular point of view, the common denominator in these different diseases appears to be the degeneration of myocytes and the stimulation of the extracellular matrix by the occurrence of cellular debris. The primary activation of macrophages was probably caused by sequestration of cellular particles from the myocytes undergoing degeneration because of either viral infections, autoimmune processes or oxygen deficiency.

It is conceivable that in this situation increased release of cytokines from macrophages and lymphocytes occurs which leads to stimulation of the capillary endothelium and therefore to expression of ICAM-1. The presence of ICAM-1 positive endothelial cells or myocytes in heart failure can further be explained by the increase of cytokines typical of the low cardiac output situation. It is, therefore, believed that the expression of adhesion molecules is part of the pathomechanism of heart failure rather than an indicator of a particular disease.

References


Cell adhesion molecules in heart failure


