Cardiac cytokine expression is upregulated in the acute phase after myocardial infarction. Experimental studies in rats

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Abstract

Objective: The proinflammatory cytokines interleukin (IL)-1β and IL-6 are supposed to be involved in various cardiovascular diseases including reperfusion injury and cardiac hypertrophy. Methods and results: In the present study, we have examined the cytokine expression from 3 h up to 12 weeks after permanent coronary artery occlusion in rats. In the first 3–12 h, there was a strong induction in IL-1β and IL-6 mRNA expression in the infarct area (up to 50-fold) as well as in the non-infarcted myocardium (up to 15-fold). From day 3 onwards the cytokine expression was not significantly altered compared to sham-operated controls. In addition, the expression of C/AATT-enhancer binding protein-β was about fourfold elevated in the first hours after myocardial infarction, but not thereafter. Furthermore, the expression of gp130 and IL-6 receptor increased significantly in the infarct area. The elevation in cytokine expression preceded the increase in matrix-metalloproteinase-9 in the infarct area as well as the increase in ANP and collagen expression in the non-infarcted myocardium. Conclusions: We suggest that IL-6 and IL-1β act synergistically in promoting resorption of the necrotic tissue, matrix remodeling and wound healing. Furthermore, they may be involved in the early induction of fibrosis and compensatory cardiac hypertrophy of the non-infarcted myocardium, but seem not to play a key role in long-term cardiac remodeling in chronic heart failure after myocardial infarction.

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1. Introduction

Large myocardial infarction (MI) causes substantial cardiac remodeling including replacement of the necrotic area by scar as well as compensatory hypertrophy and adverse fibrosis of the surviving myocardium [1]. Moreover, it leads to congestive heart failure (CHF) which is known to be associated with local and systemic elevation of both norepinephrine (NE) and pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α [2–5]. In previous work, we and others have shown that chronic adrenergic stimulation produces cardiac hypertrophy [6,7]. We also demonstrated that adrenergic stimulation evokes IL-6 expression both in vivo and in vitro [8,9]. Transgenic mice overexpressing IL-6 and the IL-6 receptor show cardiac hypertrophy [10]. IL-6 plasma levels are elevated in acute MI as well as in the reperfused myocardium after short periods of coronary artery occlusion [11]. In addition, Ono et al. [12] and Prabhu et al. [13] showed elevated myocardial expression of IL-1β, IL-6 and TNF-α up to 20 weeks after coronary artery ligation when cellular inflammatory infiltration had abated.

We have recently characterized MI in functional terms and with respect to components of the extracellular matrix (ECM) [14]. The aim of the present study was to analyze cytokine expression after MI. We tested the hypothesis that proinflammatory cytokines may be involved in wound

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healing after coronary artery occlusion. We further studied whether the expression of IL-1β and IL-6 is associated with the development of compensatory hypertrophy and reactive fibrosis in the non-infarcted myocardium.

2. Methods

2.1. Animal model

Myocardial infarctions \((n=8–16\) at each time point) were induced in female Sprague–Dawley rats by ligation of the left anterior descending coronary artery (LAD) under ether anesthesia as previously described [14]. Sham-operated animals \((n=3–4\) at each time point) underwent the same procedure except that no ligation was carried out. Heart function was measured in closed-chest spontaneously breathing rats anesthetized with thiopental sodium \((\text{Trapanal} \text{ } 60 \text{ mg/kg i.p., Byk Gulden})\) using ultraminiature catheter pressure-transducers \((\text{Millar})\) as previously described [14,15]. After the hemodynamic measurements had been obtained, the hearts were rapidly excised. The right ventricular (RV) free wall was trimmed away and the infarct area was cut from the non-infarcted left ventricle \((\text{LV})\). The hearts of sham-operated animals were also cut into three parts: the RV, the LV and a control area of the anterior region of the LV free wall. The tissue pieces were snap frozen in liquid nitrogen for RNA and protein isolation. The investigation confirms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and was approved by the appropriate State agency of Saxony.

2.2. RNase protection assay (RPA)

Probes for CCAAT/enhancer binding protein (C/EBP)-β \((\text{GeneBank accession No. X54626, position } 700–899)\), C/EBP-δ \((\text{No. M65149, pos. } 243–540)\), IL-6 \((\text{No. M26744, pos. } 133–362)\), IL-6 receptor \((\text{IL-6R, No. M58587, pos. } 917–1245)\), gp130 \((\text{No. M92340, pos. } 291–709)\), cardiotrophin-1 \((\text{CT-1, No. D78591, position } 245–554)\), matrix-metalloproteinase \((\text{MMP})\)-9 \((\text{No. U36476, pos. } 1492–1805)\), collagen type α1 (I) \((\text{No. Z78279, pos. } 3480–3906)\), collagen type α1 (III) \((\text{No. X70369, pos. } 110–299)\), GAPDH \((\text{No. M17701, pos. } 673–755)\), and acidic ribosomal phosphoprotein \((\text{ARPP})\) \((\text{No. X15096, pos. } 559–671)\) were generated by means of RT-PCR essentially as previously described [14]; 5 to 7.5 μg of total RNA were used, and protected probes were quantified using the Molecular Imager \((\text{BioRad})\). The signals of specific mRNAs were normalized to those of ARPP or L32 mRNA.

The template sets contained the following cDNA probes (probe length in bp/protected):

1. rCK1: IL-1α \((432/403)\), IL-1β \((390/361)\), TNF-β \((351/322)\), IL-3 \((315/286)\), IL-4 \((285/256)\), IL-5 \((255/226)\), IL-6 \((231/202)\), IL-10 \((210/181)\), TNF-α \((189/160)\), IL-2 \((171/142)\), Interferon γ \((156/127)\), L32 \((141/112)\) and GAPDH \((126/97)\);
2. gp130 \((475/418)\), IL6R \((382/328)\), C/EBP-δ \((353/297)\), IL-6 \((296/228)\), C/EBP-β \((258/200)\), ARPP \((143/113)\) and GAPDH \((128/82)\);
3. collagen type α1 (I) \((504/449)\), ANP \((309/234)\), collagen type α1 (III) \((310/211)\), ARPP \((143/113)\) and GAPDH \((128/82)\);
4. MMP-9 \((415/340)\), ARPP \((143/113)\) and GAPDH \((128/82)\) and
5. CT-1 \((345/309)\), ARPP \((143/113)\) and GAPDH \((128/82)\).

2.3. Rat IL-6 ELISA

Serum was prepared from 0.5-ml blood samples drawn from a tail vein under light ether anesthesia at different times after surgery. After clotting for 30 min at room temperature, the samples were centrifuged for 10 min at 4000 rpm, and the serum was collected. IL-6 was measured by ELISA according to the protocol provided by the manufacturer \((\text{BioSource})\). The minimum detectable amount of rIL-6 was <8 pg/ml.

2.4. Immunoblotting

Protein extraction and immunoblotting were carried out as described earlier [14] with only minor modifications. Affinity-purified polyclonal antibodies against rat IL-6 \((1 \mu g/ml, \text{BioSource ARC0062})\) and phospho-STAT3 \([\text{Tyr}_{705}]\) \((1:1000, \text{NEB}#9131)\) were used. After detection of phospho-STAT3 \([\text{Tyr}_{705}]\), the membranes were treated with 0.1 mol/l Glycin, pH 2.9 for 20 min and reprobed using antibodies against STAT3 \([\text{phosphorylation-state independent}]\) \((1:1000, \text{NEB}#9132)\). Goat-anti-rabbit IgG antibodies \((\text{Dianova})\) labeled with horseradish peroxidase for luminescence reaction at a dilution of 1:10 000 were used as secondary antibodies. The primary antibody was replaced by pre-immune goat serum in control experiments.

2.5. Statistical analysis

The data are expressed as mean±S.E.M. Multiple range test and Kruskal–Wallis test on ranks were used for multigroup comparison using multiple comparison pro-
3. Results

3.1. Hemodynamic measurements

All experimental animals had myocardial infarctions as confirmed by inspection of the LV myocardium and by ECG. The hemodynamic measurements, however, showed that 36% of the surviving animals had only a slight reduction in LV function (Fig. 1). Only animals with severe depression in LV function were included in this study. Depression in LV function was defined by a marked increase in LV end-diastolic pressure (LVEDP) and in RV systolic pressure (RVSP). Since the RVSP increased only from day 9 onwards (Fig. 1B), the animals up to day 9 were selected on the basis of a LV developed pressure below 110 mmHg (Fig. 1A). The hemodynamic measurements further showed a strong reduction in the rate of rise and fall in LV pressure (LVdP/dt\text{max} and LVdP/dt\text{min}, respectively) as well as in LV stroke work (not shown). RV function was measured from day 3 onwards. There was a progressive increase in RVdP/dt\text{max}, RVdP/dt\text{min} and stroke work from day 9 onwards (not shown).

3.2. Cardiac cytokine expression

Since it is well known that cytokines are induced after surgery, we also investigated a few animals without any surgery (n=3). We did not observe any differences with respect to cytokine expression between these control rats and sham-operated animals in which the surgery was done three or more days ago (not shown). Therefore, the increases in cytokine expression for 3 days and longer post-MI were given as x-fold changes from the mean value of all ‘long-term sham-operated animals’ (n=29) which best represents the normal level. Cardiac cytokine expression increased in sham-operated animals in the first 6 h after surgery (Fig. 2A, left-hand panel). Thus, we compared the samples of the MI-animals for up to 1 day after surgery to the respective control areas (MI-control, LV and RV) of time corresponding sham-operated controls.

A pronounced increase in the mRNA expression of IL-1\beta and IL-6 occurred in both the non-infarcted LV and the infarct area 6 h after LAD occlusion (Fig. 2A). Both IL-1\beta and IL-6 mRNA expression further increased in the infarct area 12 h after MI, but afterwards declined rapidly (Fig. 3). IL-1\beta and IL-6 were also elevated in the non-infarcted LV and RV but to a lesser extent (Fig. 4A,B). They declined already after 12 h. From day 3 after surgery onwards, there was no further significant increase for both cytokines either in the infarct area or in the non-infarcted LV. In addition, IL-1\alpha was detectable by RPA analysis in the infarcted and in the non-infarcted myocardium until 12 h after MI, but only in animals with MI (Fig. 2A). There was also a slight increase in TNF-\alpha mRNA expression in the infarcted and non-infarcted myocardium with a maximum elevation of about threefold around day 1 after MI. No signals were obtained for all other cytokines investigated by the rCK1 set. In contrast, transcripts of cardioprophilin (CT)-1 were readily detectable, but no significant changes occurred in the infarct area or the non-infarcted myocardium for up to 4 weeks after MI (Fig. 2B).
Fig. 2. Representative autoradiographs from RNase protection assays of cytokines (rCK1-set, A) and cardiotrophin-1 (CT-1, B) in the non-infarcted LV (LV) and in the infarct area (MI) at different times after LAD occlusion as indicated. (S) sham-operated controls. Each lane was loaded with 7.5 μg (A) or 5 μg (B) total RNA.
3.3. Expression of collagens, MMP-9, and ANP

The expression of collagens as main components of the ECM strongly increased in the non-infarcted myocardium. Collagen I mRNA was elevated first on day 1 after MI, showed maximum expression on day 3 and thereafter slowly declined (Fig. 4C). There were no differences in the increase in collagen I expression between the non-infarcted LV and RV. Furthermore, the collagen III expression showed an identical expression pattern (not shown). The MMP-9 mRNA expression was induced in the infarct area from 6 h after MI onwards (Fig. 3C). It reached maximum expression on day 1 after MI. Thereafter, it declined, but remained slightly elevated until 12 days post-MI. In the non-infarcted myocardium, very low MMP-9 expression levels were observed, and no differences were detectable when compared to sham-operated controls (not shown).

The mRNA expression of ANP as marker of hyper-
Fig. 4. Relative IL-6 (A), IL-1β (B), collagen I (C) and ANP (D) mRNA expression in the non-infarcted left and right ventricle (LV and RV, respectively) at different times after LAD occlusion as indicated. Data are expressed as x-fold changes from controls after normalization to L32 (A and B) or ARPP (C and D) mRNA. The data for collagen I mRNA in the non-infarcted LV are, in part, adapted from our previous study [14]. Values are mean±S.E.M.; n=6–12 for each group; †P<0.05 versus sham-operated controls.
trophy and activation of the fetal gene program was markedly increased in the non-infarcted LV from day 1 onwards (Fig. 4D). In the non-infarcted RV it increased from day 9 onwards.

3.4. Expression of transcription factors, gp130, and IL-6 receptor

The mRNA expression of CAATT/enhancer binding proteins (C/EBP)-β (NF-IL-6) and C/EBP-δ increased in the infarct area (Fig. 5) as well as in the non-infarcted myocardium as early as 3 and 6 h after LAD occlusion. Thereafter, both C/EBP-β and -δ rapidly declined in the non-infarcted myocardium. No differences from sham-operated controls were observed from 12 h after MI onwards. In the infarct area, both C/EBP-β and -δ reached control levels on day 1 after MI. Thereafter, no further changes were detectable for C/EBP-β (Fig. 6A). In contrast, C/EBP-δ showed a second progressive increase from day 6 after MI onwards (Fig. 6B).

Transcripts of gp130 were readily detectable in the myocardium after both MI and sham-operation (Fig. 5). No changes occurred during the first 3 weeks except for 12 h post-MI in the infarct area (Fig. 6C). After 4 weeks, gp130 mRNA expression slightly but significantly increased in the infarct area. There were no significant

Fig. 5. Representative autoradiographs from RNase protection assays of transcription factors, gp130 and IL-6 receptor (IL-6R) in the infarct area (MI) at different times after LAD occlusion as indicated. (S) sham-operated controls. Each lane was loaded with 5 μg total RNA.
Fig. 6. Relative mRNA expression of C/EBP-β (A), C/EBP-δ (B), gp130 (C) and IL-6R (D) in the infarct area (MI) and in the non-infarcted left and right ventricle (LV and RV, respectively) at different times after LAD occlusion as indicated. Data are expressed as x-fold changes from controls after normalization to ARPP mRNA. Values are mean±S.E.M.; n=6–12 for each group; †P<0.05 versus sham-operated controls.
changes in gp130 expression in the non-infarcted myocardium. In contrast, IL-6 receptor expression increased in the infarct area on day 3 after MI. It decreased thereafter, but remained slightly elevated during the observation period (Fig. 6D). In contrast, there were no significant changes in IL-6R expression in the non-infarcted LV and RV except in the LV on day 3 after coronary artery occlusion.

3.5. IL-6 protein expression and STAT3 phosphorylation

IL-6 protein markedly increased in the myocardium from 12 h to 2 days after MI (Fig. 7). Thereafter, weak signals were detectable in the MI animals as well as in the sham-operated controls. In parallel, a strong phosphorylation of STAT3 at Tyr occurred (Fig. 7). Similar but weaker signals were obtained for the non-infarcted infarcted myocardium (not shown).

3.6. Serum levels of IL-6

The serum IL-6 was 17 (±3.5) and 12 (±1.5) pg/ml in sham-operated animals (n=5 at each time point) and 30 (±4.5) and 40 (±8) pg/ml in the MI animals (n=14 at each time point) at 6 and 12 h after surgery, respectively. On day 1, minimal IL-6 levels were detected in a few but not all animals. Thereafter, no IL-6 was detectable by ELISA in the serum of all animals.

4. Discussion

4.1. Functional and morphological alterations

The severity of MI was evaluated on the basis of the hemodynamic alterations at the time of catheterization. Since an earlier morphometric analysis [16] had revealed that only hearts with infarct sizes greater than 45% had marked elevation in LVEDP and RVSP, only those animals were included in this study. For up to 9 days after MI, a LV developed pressure below 110 mmHg was used as criterion instead of RVSP (Fig. 1). We also observed marked RV hypertrophy as measured by RV weight to body weight ratio (not shown), which is well documented in various earlier studies [14–17]. LV and RV hypertrophy were further documented by a marked increase in ANP mRNA expression (Fig. 4D).

4.2. Cardiac cytokine expression after myocardial infarction

IL-1β and IL-6 mRNA were strongly induced in the myocardium after permanent coronary artery occlusion in rats. This induction persisted over the first 12 h after infarction and rapidly declined to control levels thereafter (Fig. 3). A similar increase also occurred in the non-infarcted myocardium, but to a lesser extent and for a shorter duration (Fig. 4). Also the myocardial IL-6 protein increased 12 h to 2 days after MI. This increase was accompanied by a marked increase in the phosphorylation of STAT3 at Tyr(705) indicating an activation of the JAK/STAT pathway through gp130, the signal transducing component of the IL-6 cytokine family (Fig. 7).

This increase in cytokine expression after MI is similar to that by norepinephrine [8,9]. Therefore, norepinephrine, which is strongly increased systemically and locally after MI [18], might contribute to the increased cytokine expression besides other factors like hypoxia, complement-derived factors (C5a) or TNF-α. Norepinephrine may account for the early induction in the infarct area as well as in the non-infarcted myocardium 6 h after MI. The further increase in the infarct area is likely due to invading leukocytes since the resident myocardial cells in the necrotic area have died.

Kukiellka et al. [19] found increased IL-6 mRNA in the canine myocardium after 1 h of ischemia followed by 3 h of reperfusion, but weaker signals after 4 h of permanent ischemia. Furthermore, there were no differences in the IL-6 mRNA expression after 24 h permanent ischemia compared with 1 h of ischemia followed by 24 h of reperfusion. Samples at 6 and 12 h of permanent ischemia...
were not analyzed. In addition, the highest IL-6 levels were detected in the segments displaying the greatest degree of ischemia [19]. Therefore, we speculate that IL-6 plays an important role in both permanent ischemia as well as in reperfusion injury. These data support the hypothesis that pro-inflammatory cytokines are induced in resident cardiac cells, at least in the early stage, and contribute to the initiation of the signal cascades leading to the inflammatory phase of wound healing after coronary artery occlusion.

The increase in cytokine expression preceded the strong elevation in the expression of MMP-9 mRNA in the infarcted myocardium (Fig. 3C). As we have shown recently, this was accompanied by a marked increase in gelatinolytic activity [14]. In the present study, a significant amount of IL-6 protein and the activation of its downstream signal transduction mechanism was shown (Fig. 7). This suggests that IL-6R and gp130 are expressed in sufficient amounts. Moreover, the increases in IL-6 mRNA, IL-6 protein and STAT3-phosphorylation occurred in a timely ordered fashion. Similar data on IL-1β protein are currently not available, but would provide some more relevant information on patho-physiological function. IL-1β, which is known to inhibit collagen synthesis, also promotes collagen degradation by activating expression, release and activation of MMPs in leukocytes, lymphocytes and fibroblasts [20–23]. IL-6, on the other hand, can induce ICAM-1 expression and the subsequent adhesion of leukocytes [24]. It may also contribute to transendothelial leukocyte migration by altering endothelial permeability [25,26]. Therefore, IL-6 and IL-1β may act synergistically in promoting resorption of the necrotic tissue. We suggest that this may be important for matrix remodeling and wound healing after infarction.

In the non-infarcted myocardium, the situation is different, since the resident cells survive and less leukocyte infiltration occurs. Moreover, most of the changes in the non-infarcted myocardium are very similar to the effects of norepinephrine in our previous studies on norepinephrine-induced cardiac hypertrophy in rats [6,8]. Therefore, the observed elevation in cytokine expression in the non-infarcted myocardium might be involved in the initiation of compensatory hypertrophy after MI. This is in good accordance with the observed increase in ANP expression (Fig. 4D). In a previous study, we reported RV hypertrophy measured as RV weight/body weight ratio (RVW/BW) from day 12 post-MI onwards [14]. This was paralleled by the increase in ANP expression (Fig. 4D). The LV weight data are more difficult to interpret, since the LVW/BW slightly decreased initially due to the loss of mass of the infarct area. From day 12 onwards, this parameter increased as a sign of hypertrophy. Therefore, ANP expression seems to us to be a reliable indicator of the onset of LV hypertrophy.

In the non-infarcted RV, however, there is a gap between the increase in cytokine expression and the later occurring RV hypertrophy and ANP expression. On the other hand, in both the non-infarcted LV and RV, IL-6 preceded an early and parallel increase in collagen I (Fig. 4C) and collagen III [14] expression. Therefore, we speculate that IL-6 is involved in cardiac remodeling by promoting fibrosis either directly or by inducing fibroblast proliferation. In addition to the well-known wide ranging IL-6 effects on cell growth and differentiation, a fibrogenic IL-6 activity has also been described [27–29].

Our data are in agreement with the observation of increased serum IL-6 levels as a diagnostic marker of acute MI or unstable coronary heart disease. Nevertheless, this may also reflect an acute phase reaction, since the serum IL-6 increases in parallel to the myocardial IL-6 mRNA. The elevation in myocardial IL-6 protein occurred somewhat later. The serum IL-6 might also be derived from leukocytes that are activated in the ischemic myocardium [30]. However, we did not observe increased serum IL-6 in the later phases of congestive heart failure. Also, there was only a slight but non-significant increase in IL-6 expression in the myocardium for up to 12 weeks after MI (Figs. 3 and 4). This is compatible with the results by Ono et al. [12] who measured a two- to threefold increase in IL-6 mRNA by RT-PCR 8 and 20 weeks after MI. It is, however, at variance with the findings by Prabhu et al. [13], who observed a strong increase in IL-6 mRNA as well as IL-6 protein 12 weeks after MI. The reason for this discrepancy is not clear.

The animals in our study were characterized by a depressed LV function (Fig. 1) and signs of congestive heart failure. The lack of a significant myocardial cytokine expression in these MI rats (Figs. 3 and 4), led us to re-investigate all rats with MI but nearly normal heart function which were not included in this study (open circles in Fig. 1). It turned out that cardiac cytokine expression in the myocardium of these additional animals was not different from the MI-rats which developed CHF (not shown). Interestingly, there was also no significant IL-6 increase in the myocardium derived from patients with end-stage heart failure [31]. Therefore, IL-6 seems not to play a key role in the long-term cardiac remodeling in congestive heart failure after MI. Also C/EBP-β expression is not increased at later times after MI. Moreover, IL-6R and gp130 are only slightly elevated weeks after MI (Fig. 6). This further indicates that there is no strong activation of IL-6 transcription or IL-6 action in the myocardium, especially since the IL-6 receptor complex is not thought to be re-utilized after activation by ligand binding, but needs to be newly synthesized after internalization. On the other hand, gp130 is ubiquitously expressed in almost all cells and may be sufficient for activation.

Our data are in accordance with the study by Hirota et al. [9] in which chronic activation of gp130 caused cardiac hypertrophy in transgenic mice. This activation was due to overexpression of both IL-6 and IL-6R. Therefore, other members of the IL-6 family may exert a similar effect,
since they all share gp130 for signal transduction. Cardiotrophin-1 as member of the IL-6 family was not elevated in our study (Fig. 2B), although it was incriminated to play a role after MI [32]. On the other hand, leukemia inhibitory factor was recently shown to be elevated in the myocardium of patients with end-stage heart failure [31]. We cannot completely rule out the possibility that even the slight increases in IL-6, IL-6R and gp130 may contribute to cardiac remodeling over time.

On the other hand, there might be a species dependence on the changes in inflammatory response, especially since there are important differences in the acute phase reaction, e.g. in the induction of C-reactive protein or serum-amyloid. The available data on the myocardium of mice, rats, dogs, and humans to date [11,19,30,33–36] lead to the suggestion that inflammation represents a basic mechanism. This is also emphasized by a comparable change in serum IL-6 in the acute stages after MI. The time course may vary, but the inflammation is initiated to promote repair very rapidly after injury.

Serum IL-6 is elevated in patients with CHF [5]. A similar elevation was not observed in rats, but this might be due to the low sensitivity of the available rat IL-6 ELISA. However, the source of IL-6 production remains unknown. We know from our previous studies that norepinephrine, which is also elevated in patients with CHF [2], induces IL-6 expression [8,9]. Therefore, we would like to conclude that elevated serum IL-6 in patients with CHF reflects an increased adrenergic drive and is rather a diagnostic and prognostic factor than causally related to decompensation in CHF. Norepinephrine was also shown to induce myocyte hypertrophy, fibroblast proliferation and fibrosis by direct receptor effects [8]. IL-6 was increased in this model only in the first 24 h. Murray et al. observed a prolonged IL-6 increase by treatment with isoproterenol in rats over 1 week [37], but this may be due to the different adrenergic stimulus. Contrarily, they also detected a high IL-6 expression in the myocardium 12 weeks after MI, but could not influence this by metoprolol [13]. In the current study, IL-6 was not significantly elevated after MI from day 3 onwards. This suggests that IL-6 may be involved in the early induction of cardiac remodeling but has only minor influence on long-term changes.

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