Mechanisms of Cardiac Depression Caused by Lipoteichoic Acids From Staphylococcus aureus in Isolated Rat Hearts

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Background—Lipoteichoic acid (LTA) represents a major virulence factor in gram-positive sepsis.

Methods and Results—In the present study we perfused isolated rat hearts for 180 minutes with highly purified LTA from Staphylococcus aureus. A progressive decline of left ventricular contractile function paralleled by the expression of myocardial tumor necrosis factor-α (TNF-α) mRNA and protein as well as the release of TNF-α into the perfusate was observed in LTA-perfused hearts. Employment of an anti–TNF-α antibody completely prevented the loss in contractile function. When CD14, a prominent pathogen recognition receptor, was blocked by a specific antibody, induction of TNF-α mRNA and protein release as well as the associated cardiodepression was diminished in response to LTA. Synthesis of TNF-α protein was located to interstitial cells of LTA-challenged hearts as detected by immunohistochemistry. Besides progressive cardiodepression, coronary perfusion pressure (CPP) was moderately increased in LTA-perfused hearts. This was accompanied by the release of thromboxane A₂ (TXA₂) into the perfusate and the induction of cyclooxygenase (Cox)-2 mRNA and protein in the myocardium. Blocking of TXA₂ by the nonspecific Cox inhibitor indomethacin, the thromboxane receptor antagonist daltroban, or the selective Cox-2 inhibitor NS-398 prevented the increase in CPP.

Conclusions—LTA causes cardiac depression by activating myocardial TNF-α synthesis via CD14 and induces coronary vascular disturbances by activating Cox-2–dependent TXA₂ synthesis. These phenomena may contribute to cardiac depression in gram-positive sepsis. (Circulation. 2005;112:691-698.)

Key Words: heart failure ■ thromboxane ■ bacterial toxins ■ cytokines ■ sepsis

Myocardial depression contributes to the cardiovascular dysfunction in sepsis and septic shock. Despite an elevated cardiac output, cardiac performance is deteriorated, as indicated by depressed biventricular ejection fractions and dilated ventricles.¹ Cardiodepressant effects of cytokines, predominantly tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), have been implicated in the development of cardiac depression in sepsis.² TNF-α impairs contractile performance in intact animals, isolated hearts, or cardiomyocytes either by activating the sphingomyelinase pathway³,⁴ or by releasing cardiac nitric oxide (NO) via the constitutively expressed⁵,⁶ or the inducible NO synthase.⁷ Recent studies demonstrated that the myocardial tissue itself synthesizes TNF-α in response to various challenges, including lipopolysaccharide (LPS) exposure.⁸ Additionally, sepsis-associated disturbances of the microcirculation in the myocardium, evoked by vasoactive mediators such as thromboxane A₂ (TXA₂), NO, and cysteinyl-leukotrienes, may depress cardiac function even when overall coronary blood flow is preserved.⁹–¹⁵

In experimental animals, the cardiovascular abnormalities of sepsis can be mimicked by injecting either gram-negative bacteria¹⁶ or purified LPS.¹⁷ LPS represents the most prominent pathogenicity factor in gram-negative infections and has been demonstrated to depress contractility of isolated hearts and cardiomyocytes.⁴,⁸,¹⁸ However, gram-positive bacteria, which account for at least one half of all cases of sepsis,¹⁹ do not contain LPS and yet induce the typical cardiovascular changes of the disease.²⁰ Indeed, it has recently been shown that S aureus elicits cardiac dysfunction in a septic mouse model associated with a concomitant increase in myocardial TNF-α and IL-1β synthesis.²¹ Structural components of the gram-positive cell wall, such as lipoteichoic acid (LTA) or peptidoglycan, may account for the virulence of these germs in gram-positive infections. LTA, a macroamphiphile, which consists of a poly-glycerophosphate backbone covalently...
linked to a glycolipid, has been shown to stimulate cytokine release from monocytes and macrophages, to stimulate the expression of endothelial adhesion molecules, and to cause septic shock and multiple organ failure in experimental animals.

In the myocardium of either S. aureus– or LTA-treated rats, both TNF-α and IL-1β mRNA were found to be upregulated. Like LPS, LTA has been shown to bind to CD14 and Toll-like receptors (TLRs) to induce activation of nuclear factor-κB (NF-κB), and cardiac expression of TLR2 was the prerequisite for cardiac depression associated with myocardial NF-κB activation and TNF-α and IL-1β synthesis. This may represent the prerequisite for the observation that LTA stimulates cytokine production and NO release in different cell types. Previous studies were impaired by the LPS contamination and decomposition of commercial LTA preparations. Pure and biologically active LTA was made available only recently.

Against this background, the purpose of the present study was to elucidate whether LTA from S. aureus, one of the most prevalent bacteria to cause sepsis, depresses cardiac performance of isolated rat hearts and, if so, to study the mechanisms involved. In essence, we found that coronary perfusion of highly purified and biologically active LTA induced significant depression of left ventricular performance mediated by toxin-activated cardiac TNF-α synthesis by interstitial cells. Moreover, LTA altered coronary perfusion by activating cyclooxygenase (Cox)-2–dependent TXA2 synthesis. Therefore, staphylococcal LTA is suggested to be a potent microbial pathogenicity factor to cause cardiac dysfunction in gram-positive sepsis.

Methods

Materials

The neutralizing mouse anti-rat TNF-α antibody Mab 510 was purchased from R&D (Wiesbaden-Nordenstadt, Germany), the isotype-control mouse IgGl (MOPC21) from Sigma (Deisenhofen, Germany), anti-CD14 antibody (MY4) from Coulter (Miami, Fla), indomethacin from ICN Biomedicals (Aurora, Ohio), the selective Cox-2 inhibitor NS-398 from Calbiochem (La Jolla, Calif), and the TXA2 receptor antagonist daltroban (BM 13.505) from Boehringer (Mannheim, Germany). Other materials used are stated below.

Preparation of LTA From S. aureus

LTA from S. aureus was isolated and purified as recently described. LPS contamination of the preparation was tested in a chromogenic LAL assay (QCL-1000, Bio Whittaker), in which an activity equivalent to 5 pg of LPS was found per milligram of LTA.

Isolated Heart Perfusion and Experimental Protocols

The isolated rat heart preparation has previously been described in detail. Briefly, male Wistar rats (Charles River, Sulzfeld, Germany) were heparinized (heparin, 1000 IU/kg) and anesthetized (pentobarbital, 60 mg/kg) by intraperitoneal injection. The hearts were rapidly excised and immersed in ice-cold Krebs-Henseleit buffer solution (KHBS). After the organ weight was determined, the hearts were attached to a Langendorff perfusion apparatus and were perfused at constant flow (10 mL/min per gram) with a modified KHBS containing the following (mmol/L): NaCl 125, KCl 4.5, KH2PO4 1.1, MgCl2 1.3, MgSO4 1.3, CaCl2 2 H2O 2.4, NaHCO3 25, and glucose 13.32. The perfusate was gassed with carbogen (5% CO2, 95% O2). The pH was 7.4±0.03, PO2 500±45 mm Hg (66.7±6.0 kPa), and Pco2 35±5 mm Hg (4.7±0.7 kPa) at 37°C. All hearts were initially rinsed with 150 mL KHBS in a nonecruclating mode before a switch to recirculation (total volume 50 mL).

For monitoring coronary perfusion pressure (CPP), the aortic cannula was connected to a pressure transducer (Combitrans, Braun). To measure left ventricular contractility, a latex balloon attached to a second pressure transducer was inserted into the left ventricular cavity. Left ventricular developed pressure (LVDP) was calculated as the difference between peak-systolic and end-diastolic pressure (8 to 12 mm Hg), and the maximum rate of left ventricular pressure rise (dP/dtmax) was computed by a differentiator (Schwarzer DRE 48, Picker). Hearts were paced at 320 to 360 bpm by a Stimulator P Typ 201 (Hugo Sachs Elektronik). All physiological parameters were recorded on a 12-channel polygraph (Schwarz CU 12-N, Picker).

LTA (1, 2, and 10 μg/mL) was perfused for 180 minutes. Perfusate samples for determination of TNF-α, thromboxane B2 (TXB2), and creatine kinase (CK) were taken twice before and 30, 60, 90, 120, 150, and 180 minutes after LTA application. After 180 minutes, hearts were frozen in liquid nitrogen and stored at −80°C for mRNA determination by polymerase chain reaction (PCR) and protein quantification by Western blot. For pharmacological intervention, either anti-TNF-α antibody (10 μg/mL), anti-CD14 antibody (2.5 μg/mL), indomethacin (100 μmol/L), NS-398 (25 μmol/L), or daltroban (10 μmol/L) was admixed to the perfusate 10 to 20 minutes before LTA application (2 μg/mL). Control experiments included perfusion solely with perfusate, with perfusate enriched with the respective pharmacological inhibitors, and with LTA and MOPC21. For the immunohistochemical studies, hearts were perfused for 180 and 360 minutes with either LTA (2 μg/mL) or KHBS alone. In hearts perfused for 360 minutes, no physiological parameters were recorded because left ventricular contractile function declines after such a long perfusion period.

Measurement of TNF-α, TXA2, and CK

TNF-α was measured with a rat TNF-α ELISA (Biosource). TXA2 was quantified by measuring its stable hydrolysis product TXB2 by ELISA (Cayman Chemical Company). CK was measured by routine techniques.

Measurement of NO

NO was detected as described by us previously. NO is rapidly converted to nitrite and nitrate, summarized as NOx, in oxygen-containing solutions. To monitor NOx, perfusate samples were transferred to a reaction vessel containing 80 mL of 0.1 mol/L vanadium (III) chloride in 2.0 mol/L HCl at 98°C. This solution quantitatively reduced NOx to NO. NO was removed from the reaction vessel by oxygen-free nitrogen continuously flushing through the liquid (160 mL/min), which entered a chemiluminescence detector (UPK300, UPK). Calibration was performed with known amounts of nitrite and nitrate.

Relative mRNA Quantification

Relative mRNA quantification was performed by the Sequence Detection System 7700 (PE Applied Biosystems) and real-time PCR. With application of comparative quantification (ΔCt), target gene was normalized to an internal standard gene as previously described in detail.

For internal calibration, mRNA transcribed from the gene encoding porphobilinogen deaminase (PBGD) was used. In preliminary experiments we showed that amplification efficiency of PBGD, TNF-α, and Cox-2 primer/probe sets was approximately equal and amounted to 1.0 (=100%).

cDNA Synthesis and Real-time PCR

For cDNA synthesis and real-time PCR, reagents as well as primers and probes were applied as previously described (Reference 4 and Table). Two microliters of cDNA was applied to each sample. Primers were added to a final concentration of 300 nmol/L each and hybridization probes to a final concentration of 200 nmol/L in a final volume of 50 μL. Cycling conditions were 95°C for 10 minutes,
followed by 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds.

**Western Blot Assay**

Heart tissues were homogenized in lysis buffer containing 50 mmol/L Tris-HCl, pH 7.6, 10 mmol/L CaCl₂, 150 mmol/L NaCl, 60 mmol/L NaN₃, and 0.1% wt/vol Triton X-100 with the use of a tissue homogenizer. Samples were centrifuged, and the supernatants were measured for protein content with the use of dye reagent concentrate. Extracts containing equal amounts of protein were concentrated in a tissue homogenizer. Samples were centrifuged, and the supernatants were blotted onto nitrocellulose membrane with a semidy transfer bridge. The bands were visualized with an enhanced ECL concentrate. Immunostaining was performed as described recently36 with mild modifications. In brief, rabbit polyclonal antibody against GAPDH. Protein loading was also confirmed by blotting membranes with an antibody against GAPDH.

**TNF-α Immunostaining**

Immunoenzymatic detection was performed by the alkaline phosphatase anti–alkaline phosphatase technique.35 In brief, 5-μm frozen tissue sections were air-dried and fixed in acetone for 10 minutes at room temperature. TNF-α immunostaining was performed as described recently36 with mild modifications. In brief, rabbit polyclonal anti–TNF-α antibody (1:250, ICC-TNF-9B, Innogenetics, Heiden, Germany) was used as primary antibody. Afterward, mouse anti-rabbit immunoglobulin (clone MR 12/52; 1:500, DAKO, Germany) was used as secondary antibody. The bands were visualized with an enhanced ECL detection kit and quantified by densitometry. An equal amount of protein loading was also confirmed by blotting membranes with an antibody against GAPDH.

**Cell Density Quantification**

Cell counts was performed morphometrically in left ventricular and right ventricular myocardium at ×20 objective magnification with an eyepiece grid as described.37 Overall, in 60 immunostained areas (each area measuring 0.66 mm²) of myocardial sections of both animal groups (nontreated controls, LTA-treated isolated Langendorff-perfused rat hearts), TNF-α-immunopositive cells were quantified. Results were calculated as immunopositive cells per square millimeter. Negative immunostaining controls were evaluated under the same conditions.

**Statistical Analysis**

All data are given as mean±SEM. Data were analyzed by either Student t test or 1-way ANOVA followed by Tukey honestly significant difference test when appropriate. Immunohistochemical stainings were analyzed with the Mann-Whitney U test. P<0.05 was considered significant.

**Results**

In control hearts, LVDP, the difference between peak systolic and end-diastolic pressure (Figure 1A), and the maximum rate of left ventricular pressure rise (dP/dtmax; not shown) remained stable throughout the experiments, whereas CPP rose slightly (Figure 1B). Coronary perfusion with LTA (2 μg/mL) led to a significant depression of LVDP (Figure 1A) and dP/dtmax (not shown), starting after a lag phase of 120 minutes. In addition, the increase in CPP was more pronounced in LTA-perfused hearts (2 μg/mL; Figure 1B). Higher doses of LTA (10 μg/mL) had no additional cardiodepressive effects, and lower doses (1 μg/mL) failed to induce significant changes (not shown).

Only minor amounts of TNF-α were detected in the perfusate of control hearts. In the perfusate of LTA-treated hearts, TNF-α protein started to accumulate after 120 minutes (Figure 2A). After 180 minutes of toxin perfusion, the expression of TNF-α mRNA (Figure 2B) and protein (Figure 3A) was enhanced in the myocardium. When LTA was perfused in the presence of a neutralizing TNF-α antibody, the depression of LVDP (Figure 4) and dP/dtmax (not shown) was completely prevented. In contrast, an isotype-control antibody had no effect on toxin-induced cardiac depression.

Perfusion of LTA in the presence of a CD14 antibody markedly diminished the release of TNF-α into the perfusate and the cardiac expression of TNF-α mRNA, whereas the control antibody remained ineffective (Figure 5). Moreover, the toxin-induced depression of LVDP (Figure 6) and dP/dtmax (not shown) was fully prevented.

Because immunohistochemical studies performed at the end of the 180-minute perfusion period revealed only few

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**Sequences, Amplicon Sizes, and Exon Localization of Primers and Probes**

<table>
<thead>
<tr>
<th>Primer Name</th>
<th>Sequence</th>
<th>Exon</th>
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<td>PBGD amplicon size: 135 bp</td>
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<td>PBGD forward</td>
<td>5’CCAAGTTTTTCACGATCCGCTACCA3’</td>
<td>e4</td>
</tr>
<tr>
<td>PBGD reverse</td>
<td>5’ATGTCCTGTAACCGCGCCGC3’</td>
<td>e1</td>
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<td>TNF-α reverse</td>
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<td>Cox-2 reverse</td>
<td>5’TTTGCCCAACCTTCCACCTGATCC3’</td>
<td>e5</td>
</tr>
<tr>
<td>Cox-2 hybridization probe</td>
<td>5’ATGATTTTAAGTCCACTCCATGGCCAGTCC3’</td>
<td>e6-e5</td>
</tr>
</tbody>
</table>

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PBGD amplicon size: 135 bp

**Primer Name**

- PBGD forward
- PBGD reverse
- PBGD hybridization probe

**Sequence**

- 5’CCAAGTTTTTCACGATCCGCTACCA3’
- 5’ATGTCCTGTAACCGCGCCGC3’
- 5’CCAGCTGACTCTTCCGGGTCGCCCAC3’

**Exon**

- e4
- e1
- e4
- e2-e3
- e6
- e5
- e6-e5

**Cox-2**

- Cox-2 forward
- Cox-2 reverse
- Cox-2 hybridization probe

**Sequence**

- 5’CCATCCTGGAAAAGTCGAAGTTTAT3’
- 5’TTTGCCCAACCTTCCACCTGATCC3’
- 5’ATGATTTTAAGTCCACTCCATGGCCAGTCC3’

**Exon**

- e6
- e5
- e6-e5

**Primer Name**

- PBGD
- TNF-α
- Cox-2

**Sequence**

- 5’CCAAGTTTTTCACGATCCGCTACCA3’
- 5’GTTGATCGGTCACCAACAGGA3’
- 5’CCATCCTGGAAAAGTCGAAGTTTAT3’

**Exon**

- e4
- e1
- e6

**AMPICRON**

- 135 bp
- 173 bp
- 149 bp

**Exon Localization**

- e4
- e1
- e4
- e2-e3
- e6
- e5
- e6-e5

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Langendorff-perfused rat hearts, TNF-α-immunopositive cells were quantified. Results were calculated as immunopositive cells per square millimeter. Negative immunostaining controls were evaluated under the same conditions.

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TNF-α-positive cells both in control and in LTA-perfused rat hearts, an additional set of experiments perfusing either LTA or KHBS alone for 360 minutes was performed. In those studies a significantly higher expression of TNF-α protein was detected in the myocardium of LTA-challenged hearts compared with time-matched controls (control, 2.3 ± 0.29 TNF-α-positive cells per square millimeter; LTA, 5.5 ± 0.67 TNF-α-positive cells per square millimeter). Interestingly, TNF-α protein was strictly confined to interstitial cells (Figure 7), whereas no staining was detected in cardiomyocytes or cells of myocardial arteries, arterioles, venules, and veins.

Only minor quantities of TXB₂, the stable metabolite of TXA₂, accumulated in the perfusate of control hearts throughout the observation period. However, in response to LTA there was a significant release of thromboxane into the perfusate (Figure 8A). In the myocardium of these hearts, expression of Cox-2 mRNA was increased at the end of the experiments (Figure 8B). There was also an increase in Cox-2 protein production (Figure 3B). Specific inhibition of Cox-2 by NS-398 and nonspecific inhibition of both Cox isoforms by indomethacin abolished the increase in TXB₂ in response to LTA, whereas the TXA₂ receptor antagonist daltroban had no effect. In the presence of NS-398, indomethacin, or daltroban, the slight increase in CPP caused by LTA was blocked (Figure 9).

No significant cardiac release of NO was observed in response to LTA. In both control and LTA-treated hearts, NOₓ, the stable metabolites of NO accumulated to a similar extent (2.8 ± 1.4 [control], 2.1 ± 0.8 [LTA] after 180 minutes of perfusion). In addition, no significant release of CK from the myocardium was observed in response to LTA (not shown).

**Discussion**

Cardiac depression contributes to the cardiovascular disturbances of both gram-negative and gram-positive sepsis. Whereas LPS has been suggested to depress cardiac performance in gram-negative infections, little is known about the cardiodepressant properties of gram-positive virulence factors. Against this background, the present study demonstrates that highly purified LTA from *S. aureus*, a major constituent of the gram-positive cell wall, depresses contractile performance of isolated and blood-free perfused rat hearts. In this context, cardiac TNF-α production is suggested to be a major effector of LTA-induced cardiodepression. Additionally, release of vasoactive TXA₂ by the inducible Cox-2 found in LTA-perfused hearts may aggravate the observed cardiac dysfunction.

Cardiac dysfunction observed in LTA-perfused hearts is clearly attributable to the biological activity of purified LTA and not to putatively contaminating LPS. First, the isolation procedure of the LTA used renders a purity of >99%, and only an equivalent of 5 pg of LPS was found per milligram of
LTA in a chromogenic LAL assay. Second, sterile tubing was used throughout the experiments, and the perfusate was proven to be LPS free. Third, using the same experimental setup, we recently demonstrated that LPS has to be perfused in a concentration of up to 0.1 to 1.0 µg/mL to yield comparable cardiodepressive effects.4

LTA-induced TNF-α synthesis clearly caused the loss in contractile function in the present study. The LTA-induced cardiodepression was paralleled by a marked release of TNF-α protein into the perfusate in a nearly superimposable fashion, and TNF-α mRNA and protein were strongly induced in toxin-treated hearts. When LTA was perfused in the presence of an anti-TNF antibody, the cardiac depression was completely prevented.

As shown by immunohistochemical studies, location of TNF-α protein within the myocardium was strictly confined...
to cells of the interstitial space and not to cardiomyocytes. In view of the fact that rat cardiomyocytes express CD14, TLR2, and TLR4, and have been demonstrated to produce TNF-α in response to LPS, it is somewhat surprising that LTA did not evoke TNF-α synthesis in cardiomyocytes by binding to CD14 and TLR2 on this cell type. However, to our knowledge it is at present unclear whether LTA actually activates TNF-α synthesis in adult rat cardiomyocytes and, if so, whether the LTA dose currently used suffices to do so. Moreover, in LPS-perfused feline hearts, it was recently demonstrated that the larger part of cardiac TNF-α production was provided by nonmyocyte cells rather than cardiomyocytes. The fact that no TNF-α was detectable in cardiomyocytes by immunohistochemistry does not exclude a contribution of this cell type to TNF-α production because low levels of TNF-α protein within cardiomyocytes may have escaped immunohistochemical detection. Nevertheless, under the present experimental conditions, nonmyocyte cells seem to be more susceptible to stimulation by LTA. Whether TNF-α is released from mononuclear cells within the myocardium in our experimental setup remains to be clarified.

In most cell types induction of cytokines in response to LPS is mediated by binding of LPS to pattern recognition receptors such as CD14 and TLRs. Because CD14 has been demonstrated to recognize gram-positive pathogenicity factors, such as LTA, we perfused LTA in the presence of an anti-CD14 antibody. Under these conditions, the induction of TNF-α mRNA, the release of TNF-α protein, and the associated cardiodepression were markedly diminished. This finding suggests that LTA binds to cardiac CD14 as a prerequisite of TNF-α release. The fact that blocking of CD14 did not fully prevent TNF-α release in response to LTA may indicate that other receptors, such as TLRs, or receptor-independent phenomena may also be involved. Recently, Knuefermann and coworkers demonstrated that S. aureus-induced cardiac depression associated with increased myocardial TNF-α synthesis was found only in TLR2-expressing wild-type and not TLR2-deficient mice. However, further studies are required to address this issue in more detail.

The cardiodepressive effects of TNF-α have been ascribed to different mechanisms. Release of NO from both the constitutive and the inducible NO synthase has been identi-
fied as molecular effector of TNF-α-induced cardiodepression.\textsuperscript{4-7} In our study a steady accumulation of NO\textsubscript{x}, the sum of NO degradation products, was detected in control hearts, reflecting a basal activity of NO synthase. However, no additional NO release was noticed in response to LTA, thus excluding any effects of LTA per se or LTA-induced TNF-α on NO formation. Whether alternative mechanisms, such as activation of sphingomyelinases in cardiomyocytes by TNF-α, are responsible for the observed increase on the molecular level needs further clarification.\textsuperscript{4,8}

Another remarkable finding of the present study was that coronary perfusion of LTA evoked a moderate increase in coronary vascular resistance paralleled by a significant release of TXA\textsubscript{2} into the perfusate. This moderate increase in CPP was caused by TXA\textsubscript{2} bioactivity because it was completely abolished in the presence of the nonspecific Cox inhibitor indomethacin or the thromboxone receptor antagonist daltroban. Interestingly, when NS-398, a specific inhibitor of Cox-2, was used, both the increase in CPP and the release of TXB\textsubscript{2} were abrogated, indicating that myocardial Cox-2 is upregulated in response to LTA. Corroborating this finding, Cox-2 mRNA and protein were also induced in LTA-perfused hearts. This is of particular interest because it has been recently demonstrated that cardiac Cox-2 is upregulated in pathological states such as sepsis.\textsuperscript{41} The precise pathophysiological consequence of this finding cannot be derived from our experiments, which were terminated after 3 hours of toxin perfusion. However, we speculate that the local production of vasoactive mediators in septic hearts may cause microcirculatory perfusion abnormalities, which may then contribute to myocardial dysfunction in sepsis. Such mechanism was previously demonstrated in hearts exposed to microbial exotoxins, such as staphylococcal α-toxin and Escherichia coli hemolysin.\textsuperscript{9-15}

In conclusion, the present study demonstrates that LTA from \textit{S aureus} depresses cardiac performance of isolated rat hearts by activating myocardial TNF-α synthesis. LTA is suggested to bind to cardiac CD14 as a prerequisite of TNF-α release. In addition, LTA stimulates the release of TXA\textsubscript{2} via upregulation of the inducible Cox-2, which may induce vascular disturbances within the myocardium. These phenomena may contribute to cardiovascular abnormalities in gram-positive sepsis.

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References


Cardiac dysfunction is part of the cardiovascular abnormalities of septic shock. Although the incidence of gram-positive sepsis steadily rises, the pathophysiological sequences causing this disease are not fully established. *S. aureus* represents the most prevalent gram-positive bacterium to cause sepsis. Over the past years the pathophysiological relevance of lipoteichoic acid (LTA), a major constituent of the gram-positive cell walls, has been increasingly recognized. The aim of this study may help us to understand the complex pathophysiology of gram-positive sepsis and may promote novel therapeutic strategies targeting either bacterial pathogens or their specific receptors.
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