CD14-Deficient Mice Are Protected Against Lipopolysaccharide-Induced Cardiac Inflammation and Left Ventricular Dysfunction

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Background—The molecular mechanisms responsible for sepsis-induced myocardial dysfunction remain undefined. CD14 mediates the inflammatory response to lipopolysaccharide (LPS) in various organs including the heart. In this study we investigated the role of CD14 in LPS-induced myocardial dysfunction in vivo.

Methods and Results—Wild-type and CD14-deficient (CD14-D) mice were challenged with Escherichia coli LPS. Myocardial tumor necrosis factor, interleukin-1β (IL-1β), and NOS2 induction was measured before and 6 hours after LPS challenge. Echocardiographic parameters of left ventricular function were measured before and 6 hours after LPS administration. LPS challenge induced a significant increase in myocardial tumor necrosis factor and IL-1β mRNA and protein expression in wild-type mice. In contrast, mRNA and protein levels for TNF and IL-1β were significantly blunted in CD14-D mice. An increase in NOS2 protein was noted within 6 hours of LPS provocation only in the hearts of wild-type mice. This was associated with an increase in ventricular cGMP levels. Activation of nuclear factor-κB was observed within 30 minutes of LPS in the hearts of wild-type mice but not in CD14-D mice. In wild-type mice, LPS significantly decreased left ventricular fractional shortening, velocity of circumferential shortening, and dP/dt max. LPS-treated CD14-D mice maintained normal cardiac function.

Conclusions—These results suggest that CD14 is important in mediating the proinflammatory response induced by LPS in the heart and that CD14 is necessary for the development of left ventricular dysfunction during LPS-induced shock in vivo. (Circulation. 2002;106:2608-2615.)

Key Words: immune system ■ shock ■ inflammation ■ echocardiography

During Gram-negative bacteremia, the release of lipopolysaccharide (LPS), a component of the outer membrane of the bacteria, induces a dysregulated immune response that is characterized by the overproduction of tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), and nitric oxide (NO).1,2 Over the last decade, it has become clear that myocardial depression is a complication of human septic shock.3–6 A circulating myocardial depressant factor in septic patients was proposed more than 50 years ago, but it was not until the late 1980s that myocardial dysfunction was linked to a serum factor.4 Kumar et al7 were the first to demonstrate that the negative effects on myocardial function in sepsis were mediated, at least in part, through TNF and IL-1β. Giroir et al8 and Kapadia et al9 demonstrated that local myocardial TNF levels increase after LPS challenge and contribute to the development of left ventricular (LV) dysfunction. Recently, we reported that Toll-like receptor 4 (TLR4) is involved in the induction of myocardial TNF, IL-1β, and NOS2 after LPS administration.10 More importantly, Nemoto et al11 demonstrated that TLR4-deficient mice are protected against the development of LV dysfunction in a murine model of LPS-induced shock. Although these studies have provided new insights into the pathogenesis of LPS-induced cardiac depression, the mechanisms for LPS-induced LV dysfunction remain incompletely defined.

TLR4 is clearly required for a strong induction of proinflammatory cytokines and other inflammatory mediators by LPS; however, no evidence of direct binding of LPS to TLR4 has been demonstrated. Studies designed to identify molecules on the cell surface that specifically bind LPS have identified CD14.12,13 A GPI-anchored glycoprotein expressed on the surface of most myeloid cells and other cell types, including cardiac myocytes.13–15 In vitro studies indicate that the strong proinflammatory response of monocyte/macroph...
phages and neutrophils to LPS requires binding of LPS to CD14 and, at a minimum, TLR4/MD2 for signaling. A role for CD14 as a primary mediator of LPS-induced shock was initially demonstrated by using transgenic mice overexpressing human CD14. These mice were hypersusceptible to LPS and had increased mortality rates after LPS challenge. Haziot et al later demonstrated that CD14-deficient mice were resistant to LPS-induced shock and had a significantly diminished production of proinflammatory cytokines. Although CD14 mediates many of proinflammatory responses induced by LPS, additional cell surface molecules, such as CD11b, may also play a role in LPS signaling. Previous studies from this laboratory have shown that the absence of TLR4 abrogated some but not all proinflammatory responses induced by LPS in the heart. These findings suggested the existence of other functional receptors within the myocardium. Accordingly, in this study we sought to determine whether CD14 plays a role in the pathogenesis of LPS-induced cardiac inflammation and LV dysfunction.

**Methods**

**Experimental Protocol**

We studied male and female (8 to 10 weeks of age) C57BL/6 mice (wild type; Jackson Laboratories, Bar Harbor, Maine) and CD14-deficient (CD14-D) mice, back-crossed 8 times onto a C57BL/6 background. CD14-D mice were generated as described elsewhere. Mice were injected intraperitoneally with 25 mg/kg *Escherichia coli* LPS (O111:B4; Sigma) or pyrogen-free PBS (Gibco BRL). Mice (n = 3 to 5/time point) were killed, and the hearts were harvested at 0.5, 1, 2, 4, and 12 hours after LPS challenge for determination of TNF and IL-1β gene expression and at 1, 2, 4, and 12 hours for cytokine protein production. All studies were performed in compliance with guidelines of the Institutional Animal Care and Use Committee at Baylor College of Medicine.

**CD14 Expression in Myocardial Tissue**

Myocardial proteins from whole hearts were isolated as previously described. Proteins were separated on 10% (CD14) or 8% (TLR4/TLR2) SDS-polyacrylamide gels. The membranes were immunoblotted with antibodies to CD14 (1:500; Transduction Laboratories), TLR4 (1:200; Santa Cruz), and TLR2 (1:200; eBioscience). Myocardial CD14, TLR4, and TLR2 expression was detected with the ECL-Plus Western blotting detection kit (Amersham).

**Ribonuclease Protection Assay**

TNF and IL-1β gene expression was determined by ribonuclease (RNase) protection assay system, as previously described (RiboQuant, Pharmingen). Signals were quantified through the use of Image QuaNT software (Molecular Dynamics) and normalized to L32.

**Myocardial TNF and IL-1β ELISA**

Hearts were harvested at specific times after LPS administration, and homogenates were prepared by the method of Baumgarten et al. Myocardial TNF and IL-1β protein levels were measured by enzyme-linked immunosorbent assay (R&D Systems). Data are expressed as picograms per milligram of protein.

**Myocardial NOS2 Protein Expression**

Proteins were separated on 8% SDS-polyacrylamide gel under denaturing conditions. The membrane was immunoblotted with a rabbit anti-NOS2 antibody (1:500; Sigma). The NOS2 expression was detected with ECL-Plus Western blotting detection kit (Amersham).

**Characterization of LV Structure and Function in CD14-D Mice After LPS Challenge**

**2-D Echocardiography**

Mice were anesthetized intraperitoneally with a mixture of ketamine (100 mg/kg), xylazine (2.5 mg/kg), and heparin (5000 U/kg). Echocardiographic measurements were obtained in wild-type (n = 5) and CD14-D (n = 5) mice before and 6 hours after LPS challenge, with the use of a 15-MHz linear transducer (Acuson Sequoia Cardiac System). Fractional shortening (FS) and velocity of circumferential fiber shortening (Vcf) were calculated as previously described.

**Hemodynamic Assessment of LV Function**

Measurements of LV function were obtained 6 hours after LPS injection. LV pressure, heart rate (HR), and the positive derivative of LV pressure with respect to time (+dP/dtHmax) were determined as previously described. Atrial pacing in CD14-D mice was achieved by advancing a 1F bipolar muscle pacing catheter (EP118 to 2, NuMED, Inc) into the right atrium. Measurements of mean arterial pressure (MAP), systemic vascular resistance (SVR), and central venous pressure were obtained at 6 hours after diluent (n = 5) or LPS, as previously described.

**Statistics**

Data are expressed as mean ± SEM. ANOVA followed by Bonferroni-corrected *t* test was used to determine significant differences in LPS-induced cytokine gene and protein. A nonpaired *t* test was used to assess baseline differences between wild-type and CD14-D mice and differences in cardiac function between wild-type and CD14-D mice after LPS administration. Hemodynamic data were compared among the three groups by means of ANOVA; where appropriate, a post hoc Neuman-Keuls test was performed. A probability value <0.05 was considered statistically significant.

**Results**

**CD14 Expression in Myocardial Tissue**

We first documented that CD14 protein was expressed in the myocardium of wild-type mice. Figure 1A shows that in untreated mice, CD14 is expressed at low levels in wild-type mice. However, LPS induced an increase in myocardial CD14 expression within 4 hours in wild-type mice (Figure 1A). CD14 was not detected in myocardial extracts from CD14-D mice. In contrast, TLR4 and TLR2 were constitutively expressed in wild-type and CD14-D mice and did not change in response to LPS challenge (Figure 1, B and C). Thus, these studies document the presence of an intact CD14/TLR4/TLR2 system in the adult mammalian heart.
Role of CD14 in the Induction of Myocardial TNF and IL-1β After LPS Challenge

To determine the role of CD14 in the expression of myocardial proinflammatory cytokines, TNF and IL-1β gene and protein expression were measured in both wild-type and CD14-D mice after LPS administration. Figure 2A illustrates the time course of LPS-induced TNF-α and IL-1β mRNA expression. LPS induced a rapid and robust increase in TNF and IL-1β mRNA transcripts (Figure 2A) in the hearts of wild-type mice. TNF mRNA upregulation was maximal at 30 minutes after LPS challenge in wild-type mice, whereas peak IL-1β mRNA expression occurred 1 hour after injection. LPS also induced the expression of TNF and IL-1β (Figure 2B) in the myocardium of CD14-D mice; however, the expression of both cytokines was delayed when compared with wild-type mice (Figure 2, A and B). In addition, the magnitude of the response for both TNF and IL-1β was attenuated (Figure 2, C and D). The effects on the expression of TNF and IL-1β mRNA in both groups of mice were verified by means of protein-free LPS, prepared as described by Manthey et al.²⁴

Figure 3 shows that the kinetics of TNF and IL-1β protein production paralleled the upregulation of TNF and IL-1β mRNA.
mRNA transcripts in the heart after LPS administration. Myocardial TNF protein levels were significantly higher \( (P<0.05) \) at 1 and 2 hours after LPS in wild-type mice. Peak TNF production was \( \approx 10 \) -fold higher (31.1 pg/mg versus 3.85 pg/mg) and occurred earlier (1 hour versus 2 hours) in wild-type mice when compared with CD14-D mice. Tissue levels of IL-1β also were also significantly greater in wild-type mice. In keeping with previous reports, peak serum TNF levels 1 hour after LPS challenge were significantly higher in wild-type mice when compared with CD14-D mice (9.6 ± 1.3 ng/mL versus 0.679 ± 0.328 ng/mL; \( P<0.05 \)).

**Myocardial NOS2 Protein Expression and cGMP Production During Endotoxic Shock**

Recent studies suggest that NO may contribute to cardiac depression in a mouse model of endotoxic shock. We compared myocardial NOS2 protein expression after LPS challenge in wild-type and CD14-D mice. Before LPS provocation, extracts from both wild-type and CD14-D mice had undetectable NOS2 protein (Figure 4A). After LPS, NOS2 was markedly increased at 6 and 12 hours in myocardial extracts from wild-type mice, whereas NOS2 was not detectable in extracts from CD14-D mice. As shown by the group data in Figure 4B, myocardial cGMP levels increased significantly \( (P<0.05; \text{at 6 hours}) \) in LPS-treated wild-type mice but not in CD14-D mice.

**Myocardial NF-κB Activation After LPS Administration**

Figure 5 illustrates the time course of LPS-induced myocardial NF-κB binding activity. A robust increase in NF-κB–DNA binding activity was observed in the hearts of wild-type mice within 30 minutes of LPS provocation that persisted for up to 12 hours. In contrast, in CD14-D mice, myocardial NF-κB–DNA binding activity was not detected until 2 hours after LPS injection and was back to baseline by 12 hours. The composition of the LPS-activated NF-κB complex consisted predominantly of p65 and p50 heterodimers, as determined by supershift assays. The specificity of the NF-κB–DNA complexes was confirmed by displacement of the NF-κB complex in the presence of \( \times 50 \) excess unlabeled NF-κB oligonucleotide.

**Characterization of LV Structure and Function in CD14-D Mice**

Table 1 summarizes the measurements of LV structure and function in wild-type mice (n=5) and CD14-D (n=5) mice.

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**Figure 4.** Myocardial NOS2 protein expression. A, Western blot analysis of NOS2 expression after LPS injection. Blot is representative of 3 independent experiments. B, Myocardial cGMP levels at baseline and 6 hours after LPS challenge \( (*P<0.05) \).

**Figure 5.** Myocardial NF-κB activation is impaired in LPS-challenged CD14-D mice. Crude nuclear extracts were prepared from wild-type and CD14-D mice at indicated times after LPS. Results are representative of 3 independent experiments.
Characterization of LV Function in CD14-D Mice After LPS Administration

Table 2 summarizes the hemodynamic measurements in diluent- or LPS-treated wild-type and CD14-D mice (n=5/group). All measurements were performed 6 hours after treatment. There was a significant difference in HR between LPS-treated wild-type mice and LPS-treated CD14-D mice. Six hours after LPS challenge, wild-type mice had decreased MAP and an increase in SVR when compared with LPS-treated CD14-D mice. Importantly, the HR, MAP, and SVR were significantly different between diluent-treated and wild-type mice and LPS-treated CD14-D mice. There were no differences in these parameters when comparing diluent- or LPS-treated CD14-D mice.

Given the observed differences in HR between LPS-treated wild-type and CD14-D mice and the fact that LPS can also alter LV afterload, we assessed myocardial function by using an index of contractility that is not affected by afterload: LV dP/dt max. As shown in Table 3, a significant (P<0.05) difference was noted in LV peak systolic pressure between LPS-treated wild-type mice and LPS-treated CD14-D mice that underwent atrial pacing. In addition, the +LV dP/dt max was significantly depressed (P<0.05) in the LPS-treated wild-type mice when compared with LPS-treated CD14-D mice.

2-D Echocardiographic Assessment of LV Function

Figure 6 shows representative echocardiograms of wild-type and CD14-D mice before (Figure 6, A and B) and 6 hours after LPS challenge (Figure 6, C and D). The extent of FS (Figure 6E) and the Vcf (Figure 6F) were significantly (P<0.05) depressed in the LPS-treated wild-type mice when compared with LPS-treated CD14-D mice. Of note, there were no significant differences in FS or Vcf when comparing CD14-D after LPS challenge and wild-type mice before LPS administration. The results of group data (n=5/group) showed that there was a significant (P<0.05) increase in end-systolic dimension (ESD) in the LPS-treated wild-type mice (3.02±0.05 mm) when compared with LPS-treated CD14-D mice (2.48±0.17 mm). Furthermore, the increase in ESD in the wild-type mice occurred despite a fall in MAP (Table 2), suggesting that the increase in ESD reflected a decrease in contractility.

Discussion

The results of this study suggest that CD14 is necessary for the development of LPS-induced LV dysfunction. Two major lines of evidence support this conclusion. First, LPS administration resulted in a significant depression of ejection phase indexes of contractile function (%FS and Vcf) in wild-type mice, whereas there was no significant change in these parameters in the CD14-D mice. Indeed, ejection phase indexes of contractility were not significantly different between LPS-treated CD14-D mice and wild-type mice that were not treated with LPS (Figure 6, E and F). Second, two hemodynamic indexes of LV systolic function, including peak +dP/dt and peak developed LV systolic pressures were significantly depressed in wild-type mice when compared with LPS-treated CD14-D mice (Table 3). Importantly, the observed differences in contractile function in the wild-type

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Table 1: Baseline Physiological and Echocardiographic Measurements in Wild-Type and CD14-D Mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild Type</th>
<th>CD14-D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>20±0.7</td>
<td>23±1.1</td>
<td>0.02</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>271±12</td>
<td>297±14</td>
<td>0.17</td>
</tr>
<tr>
<td>EDD/BW, cm/g</td>
<td>0.018±0.001</td>
<td>0.017±0.001</td>
<td>0.22</td>
</tr>
<tr>
<td>ESD/BW, cm/g</td>
<td>0.012±0.0005</td>
<td>0.012±0.0004</td>
<td>0.28</td>
</tr>
<tr>
<td>LV mass/BW, mg/g</td>
<td>3.3±0.07</td>
<td>2.94±0.24</td>
<td>0.17</td>
</tr>
<tr>
<td>r/h ratio</td>
<td>2.8±0.2</td>
<td>2.8±0.1</td>
<td>0.83</td>
</tr>
<tr>
<td>%FS</td>
<td>31.6±1.2</td>
<td>32.1±2.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Vcf, circ/s</td>
<td>5.78±0.16</td>
<td>6±0.3</td>
<td>0.35</td>
</tr>
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</table>

All data are mean±SEM; n=5. EDD indicates end-diastolic diameter; r/h ratio, ratio of LV radius to LV wall thickness.

Table 2: Hemodynamics in Wild-Type and CD14-D Mice Before and After LPS Administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild Type+LPS</th>
<th>CD14-D+LPS</th>
<th>P</th>
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<tr>
<td>HR, bpm</td>
<td>552±22</td>
<td>526±21</td>
<td>0.11</td>
</tr>
<tr>
<td>LV peak systolic pressure, mm Hg</td>
<td>79.9±3.3</td>
<td>105.3±6</td>
<td>0.006</td>
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<tr>
<td>dP/dt max, mm Hg</td>
<td>5143±451</td>
<td>9065±1076</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All data are mean±SEM; n=5.

Table 3: Characterization of Wild-Type and CD14-D Mice After LPS Administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild Type</th>
<th>CD14-D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>290±29</td>
<td>552±22</td>
<td>0.001</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>73.0±1.48</td>
<td>55.0±1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>SVR, dyn/cm5</td>
<td>303669±5748</td>
<td>412326±11402</td>
<td>0.001</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>3.3±0.723</td>
<td>2.1±0.458</td>
<td>0.009</td>
</tr>
</tbody>
</table>

All data are mean±SEM; n=5. CVP indicates central venous pressure.

*P<0.05 compared with diluent-treated wild-type mice (Neuman-Keuls).
†P<0.05 compared with LPS-treated wild-type mice (Neuman-Keuls).
mice and the CD14-D mice did not appear to be secondary to baseline differences in LV structure nor LV function (Table 1). Moreover, the differences in LPS-induced contractile dysfunction in the wild-type mice and the CD14-D cannot be explained readily by differences in the force-frequency relation, insofar as the HR response was significantly greater in the LPS-treated wild-type mice compared with the CD14-D mice, which would have favored increased contractile function in these animals (Table 2). Although there were significant differences in SVR in the CD14-D and wild-type mice, the increased systemic vascular resistance observed in wild-type mice could not have accounted for the depressed dP/dt in these mice because this index of contractility is afterload-independent. Although the mechanism for the observed difference in contractile function in the wild-type and CD14-D mice is not known, the results of this study strongly suggest that the blunted and/or delayed expression of proinflammatory mediators, including TNF, IL-1β, and NO, may be responsible for the preserved LV function in the LPS-treated CD14-D mice. In agreement with the differences noted in inflammatory expression, the activation of myocardial NF-κB also was delayed in LPS-treated CD14-D mice (Figure 5). Thus, these studies suggest that although CD14 is not necessary for LPS-induced expression of inflammatory mediators, CD-14 does play an important role in augmenting the expression of inflammatory mediators in the heart after LPS provocation. Interestingly, we have observed similar findings in terms of blunted expression of proinflammatory mediators (TNF, IL-1β, and NO) in the face of preserved LV function in LPS-treated mice that are defective in TLR-4 mediated signaling.11 Taken together, the findings from the present study along with previous reports from this laboratory suggest that the presence of both CD14 and TLR4 are indispensable for LPS-induced LV dysfunction. Moreover, given that the expression of CD14 appears to be inducible in the heart, whereas TLR4 is constitutively expressed (Figure 1), the results of this study suggest that the expression of CD14 in the heart may be one of several factors that influence the duration and degree of LPS-induced LV dysfunction in vivo.

The recognition of microbial pathogens is mediated by a set of germ-line encoded receptors that are referred to as pattern recognition receptors. These receptors recognize conserved molecular patterns (pathogen-associated molecular patterns or PAMPS) shared by large groups of microorganisms.26 CD14 and TLRs are known to function as pattern-recognition receptors. Until recently, CD14 and TLRs had primarily been described in cells of the immune system; however, it is now known that they are also expressed in heart, where they may play a role in the pathogenesis of sepsis-induced myocardial dysfunction.11,15,27 It has been proposed that the cellular responses induced by LPS occur through the binding of LPS to CD14, with subsequent signal transduction via TLR4. In previous studies, it has been shown that macrophages from CD14-D mice are at least 4 orders of magnitude less responsive, in terms of TNF production, to

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Figure 6. Echocardiographic assessment of effects of LPS administration. LV function in wild-type (WT) and CD14-deficient (CD14-D) mice was assessed before (A and B) and 6 hours after (C and D) LPS by 2-D–directed M-mode echocardiography. E, Group data for LV FS at baseline and after LPS challenge. F, Group data for velocity of circumferential fiber shortening at baseline and after LPS challenge. One-way ANOVA showed overall significant difference (P=0.0011) in FS and Vcf between groups. (*P<0.05 compared with LPS-treated wild-type mice).
LPS than macrophages from wild-type mice. In this regard, our data indicate that expression of myocardial CD14 is also necessary for maximal cytokine expression in the heart after LPS challenge in vivo. Furthermore, we also show that LPS provocation leads to increased CD14 expression in the hearts of wild-type mice. In contrast to the effect on CD14, LPS administration did not augment the myocardial expression of TLR4 in either wild-type or CD14-D mice. Taken together, these findings suggest that CD14 may be a key regulator of cardiac proinflammatory cytokine and NOS2 expression and therefore may play a critical role in the pathogenesis of LPS-induced LV dysfunction.

Another interesting observation of this study was that LPS-induced proinflammatory cytokine expression and NF-κB activation were delayed/blunted rather than abrogated in the hearts of the CD14-D mice. These findings may be explained, at least in part, by LPS signaling by TLR4. Studies have shown that at low concentrations of LPS (<1000 ng/mL), both membrane-bound CD14 and TLR4 are required for significant TNF induction. However, at high LPS concentrations, low levels of TNF can be induced in the presence of TLR4 alone. Although TLR2 was initially thought to function as an LPS receptor, studies in TLR2-deficient mice indicate it does not play a major role in the physiological responses to LPS. Nonetheless, recent studies have shown that LPS and TLR2 are capable of interacting and inducing cellular activation in nonmyocyte cell types. Furthermore, MD-2 also physically associates with TLR2, albeit the interaction is weaker than with TLR4, leading to enhanced TLR2-mediated responses to various forms of LPS, including protein-free LPS. Finally, we cannot formally exclude that the response to LPS in the hearts of CD14-D mice are mediated through CD14-independent signaling pathways. In this regard, recent studies have shown that heat shock shock proteins 70 and 90 can bind LPS and mediate TNF production. Whether these heat shock proteins, which are known to be expressed by cardiac myocytes, are involved in LPS recognition in the heart is not known. In conclusion, this study shows for the first time that CD14 is necessary for the development of LPS-induced myocardial dysfunction in the adult mammalian heart. As current data suggest that therapies aimed at neutralizing the effects of proinflammatory cytokines are unlikely to be successful in ameliorating the organ dysfunction associated with Gram-negative sepsis, the findings reported here may have potential clinical implications. In this regard, Verbon et al. have demonstrated for the first time that a recombinant chimeric monoclonal antibody to human CD14 inhibits systemic symptoms and proinflammatory cytokine responses in healthy humans challenged with LPS. Accordingly, an important unanswered question that arises from the present study is whether antibodies directed at CD14 will ameliorate and/or reverse the deleterious effects of LPS on cardiac function.

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References


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