A New Approach to the Development of Anti-ischemic Drugs
Substances that Counteract the Deleterious Effect of Lysophosphatidylcholine on the Heart

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SUMMARY
Lysophosphatidylcholine (LPC) is an amphiphilic metabolite that can be produced from membrane-phospholipids by activation of phospholipase A₂ (PLA₂), and it accumulates in the heart during ischemia and reperfusion. It is known that LPC is an arrhythmogenic substance. Recent studies have revealed that LPC produces mechanical and metabolic derangements in perfused working rat hearts, and Ca²⁺-overload in isolated cardiac myocytes. Thus, LPC possesses an ischemia-like effect on the heart. LPC accumulated in the myocardium activates phospholipase A₂, establishing a vicious circle; i.e. LPC itself has an ability to produce another LPC. Therefore, a drug that has an anti-LPC effect would protect or improve ischemia/reperfusion damage. This article will review the effect of LPC in relation to ischemia, and consider a possibility of developing new anti-ischemic drugs on the basis of the anti-LPC action. (Jpn Heart J 1997; 38: 11-25)

Key words: Lysophosphatidylcholine, Free fatty acid, Ischemia reperfusion, anti-ischemic drugs

ISCHEMIA and reperfusion of the heart produce myocardial damage. Although the mechanism of ischemia/reperfusion damage of the heart is not well known, there is a common understanding that Ca²⁺-overload is the final step in the events induced by ischemia/reperfusion, and that the Ca²⁺-overload is probably responsible for the ischemia-reperfusion damage. By what mechanism does ischemia/reperfusion induce Ca²⁺-overload? There are some candidates for the etiology of ischemia/reperfusion-induced Ca²⁺-overload; one is reduction of the tissue levels of high-energy phosphates including adenosine triphosphate...
(ATP) and the other is production of free radicals. In this mini review we propose that lysophosphatidylcholine (LPC) is also one of the candidates responsible for Ca\(^{2+}\)-overload during ischemia and reperfusion, and that substances that counteract the effect of LPC can be new anti-ischemic drugs.

**Why is LPC Important to Produce Ischemic Damage?**

**Chemistry of LPC:** LPC is produced by activation of the enzyme phospholipase A\(_2\) (PLA\(_2\)) from phosphatidylcholine, one of the major membrane-phospholipids\(^1\) (Figure 1). In phosphatidylcholine, the hydroxyl groups at the first and second positions of glycerol are esterified to the carboxyl groups of two long-chain fatty acids (hydrocarbon tails). The hydroxyl group at the third position of the glycerol backbone is esterified to phosphoric acid to which choline is attached (polar head). The PLA\(_2\) releases a long-chain fatty acid (usually unsaturated fatty acids such as arachidonic acid) from the second position of the glycerol backbone, and the remaining structure with one hydrocarbon tail is called LPC. Therefore, one molecule of free fatty acid (FFA) and one molecule of LPC are produced from one molecule of phosphatidylcholine by activation of PLA\(_2\).

**LPC accumulates in the myocardium during both ischemia and reperfusion:** Under physiological conditions, LPC is reacylated to form phosphatidy-

![Figure 1. Production of lysophosphatidylcholine by activation of phospholipase A\(_2\) (PLA\(_2\)).](image-url)
Figure 2. Metabolic pathway of lysophosphatidylcholine (LPC). Under ischemic conditions, PLA₂ is activated and other enzymes (lysophospholipase, acyltransferase and fatty acyl CoA synthetase) are inhibited. Therefore, LPC and free fatty acids (FFA) accumulate in the ischemic myocardium.

Table 1. Accumulation of LPC in Ischemic and Reperfused Myocardium

<table>
<thead>
<tr>
<th>Species</th>
<th>Condition</th>
<th>Increase in LPC (µM)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine hearts</td>
<td>ischemia (8 min)</td>
<td>23</td>
<td>Shaikh and Downer, 1981³)</td>
</tr>
<tr>
<td>Perfused rat hearts</td>
<td>ischemia (30 min)</td>
<td>110</td>
<td>Otani et al., 1989⁷)</td>
</tr>
<tr>
<td></td>
<td>ischemia (30 min) + reperfusion (30 min)</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Cat hearts</td>
<td>ischemia (10 min)</td>
<td>255</td>
<td>Corr et al., 1982⁴)</td>
</tr>
<tr>
<td>Human hearts</td>
<td>pacing-induced ischemia</td>
<td>109 (coronary sinus blood)</td>
<td>Sedlis et al., 1993⁷)</td>
</tr>
</tbody>
</table>

The concentration of LPC was estimated from the tissue content.

Lysine by fatty acyl CoA synthetase, or further metabolized to glycerophosphorylcholine by lysophospholipase (Figure 2). Under ischemic conditions, however, fatty acyl CoA synthetase is inhibited because of the decrease in ATP², which is necessary for reacylation of LPC. In addition, during ischemia lysophospholipase is inhibited⁶ because of acidosis and accumulation of FFA. Therefore, LPC accumulates in the ischemic myocardium. Shaikh and Dower³ reported that ischemia increased the tissue LPC level by 23 µM in porcine hearts, and Corr et al.⁴ reported that ischemia increased the tissue LPC level by 255 µM in cat hearts. Activation of PLA₂, which is activated by the increase in intracellular Ca²⁺ concentration ([Ca²⁺]i)², is also important in the production of LPC.

If the ischemic damage is irreversible, reperfusion of the ischemic myocardium inflicts damage to the heart to a greater extent (reperfusion injury). During both ischemia and reperfusion, there is an increase in [Ca²⁺]i,⁵,⁶ and therefore PLA₂ can be activated during both ischemia and reperfusion. Hence LPC accumulates during both ischemia and reperfusion. Otani et al.⁷ reported that the increase in the level of LPC in the cardiac tissue induced by ischemia was 109 µM and that induced by reperfusion was much higher (230 µM) in isolated perfused rat hearts. In a clinical study, Sedlis et al.⁸ reported that the concentration of LPC in the coronary sinus blood increased from 70 µM to 180 µM after
cardiac ischemia, which was induced by electrical pacing of the heart. Table I summarizes the reported data of the degree of accumulation of LPC in the myocardium during ischemia/reperfusion. These data demonstrate that LPC accumulates during both ischemia and reperfusion in the myocardium.

**Effect of LPC on the cell membrane and arrhythmogenic property of LPC:**

It is known that LPC, which accumulates in the ischemic and reperfused heart, is an arrhythmogenic substance. Because LPC is a metabolite of membrane-phospholipids, the physicochemical properties of the cell membrane may change after an increase in the level of LPC in the myocardium. In addition, LPC that has accumulated in cytoplasm or extracellular space can easily associate with biological membranes because of its amphiphilic property. Fink and Gross have reported that LPC changes the sarcolemmal molecular dynamics and increases membrane fluidity. Many studies have revealed that LPC inhibits the Na⁺, K⁺-ATPase and also inhibits the inactivation phase of the voltage-dependent Na⁺ channel, and increases the non-selective cation current in the cell membrane. Thus, it seems that LPC has multiple effects on biological membranes, and that these multiple effects of LPC may contribute to its arrhythmogenic effects.

**Effect of Exogenous LPC on Cardiac Function and Metabolites**

**Comparison between exogenous LPC-induced damage and ischemic damage:** Recent studies have revealed that LPC has not only arrhythmogenic effects but also additional deleterious effects on cardiac function and metabolism. The results of our recent study indicate that the effects of LPC on cardiac function and metabolism are comparable with those induced by ischemia. Figure 3 illustrates the effects of exogenous LPC on cardiac function, the levels of high-energy phosphates and those of major FFAs in the cell membrane in isolated working rat hearts. Perfusion with exogenous LPC (10 μM) for 5 min markedly decreases cardiac function, and cardiac function that has been decreased by LPC does not recover even after washout of LPC. The levels of ATP and creatine phosphate (CrP) in the myocardium decrease during perfusion with LPC, and they do not recover even after washout of LPC. The level of lactate increases during perfusion with LPC and also after washout of LPC. The FFAs, including arachidonic acid, accumulate in the heart during perfusion with LPC, and the FFA levels further increase after washout of LPC. These changes are similar to those induced by ischemia and reperfusion in isolated working rat hearts (Figure 4), although there are some differences between exogenous LPC and ischemia; the levels of ATP and CrP that have been decreased by ischemia recover after reperfusion, whereas those of ATP and CrP that have been decreased by LPC do
Figure 3. Effects of exogenous LPC (10 μM) on the mechanical function and the tissue levels of metabolites in perfused working rat hearts. a: Changes in rate-pressure product in the presence (●) or absence (□) of LPC. LPC was infused for 5 min. “Working” means establishment of working heart perfusion. Note that LPC decreased the rate pressure product markedly. b: Changes in the tissue levels of ATP, creatine phosphate (CrP), and lactate induced by LPC. c: Changes in the tissue levels of free fatty acids (palmitoleic, arachidonic and stearic acids) induced by LPC. In b and c, abbreviations are as follows. Control; hearts were freeze-clamped in the absence of LPC. LPC 5 min; hearts were freeze-clamped immediately after the end of application of LPC for 5 min. LPC 25 min; hearts were freeze-clamped immediately after the end of application of LPC for 25 min. LPC 25 min + KHB 20 min; hearts were freeze-clamped immediately after the end of perfusion with Krebs-Henseleit bicarbonate (KHB) solution for 20 min, which was preceded by application of LPC for 25 min. Note that washout of LPC for 25 min did not restore the tissue levels of metabolites that had been changed by LPC.
Figure 4. Effects of ischemia (15 min) and reperfusion (20 min) on the mechanical function and the tissue levels of metabolites in perfused working rat hearts.\(^a\) a: Changes in rate pressure product. b: Changes in the tissue levels of ATP, creatine phosphate (CrP), and lactate induced by ischemia and reperfusion. c: Changes in the tissue levels of free fatty acids (palmitoleic, arachidonic and stearic acids) induced by ischemia and reperfusion. In b and c, abbreviations are as follows. Non-ischemia; hearts were freeze-clamped in the absence of ischemia. Ischemia; hearts were freeze-clamped immediately after the end of ischemia. Reperfusion; hearts were freeze-clamped immediately after the end of reperfusion. Note that these changes are similar to those induced by exogenous LPC (see Figure 3).

not recover or further decrease after removal of LPC. The level of lactate that has been increased by ischemia decreases after reperfusion, whereas the level of lactate that has been increased by LPC further increases after removal of LPC.
Thus, exogenous LPC produces ischemia/reperfusion-like changes except that the effects of exogenous LPC continue even after washout of LPC. This may be due to the amphiphilic property of LPC; LPC associates with the sarcolemma and the membrane-associated LPC may not be removed even after washout of LPC.

**Why does exogenous LPC decrease the tissue levels of ATP and CrP?:** One possible mechanism for the LPC-induced decrease in the levels of ATP and CrP is that LPC affects oxidative phosphorylation in the cardiac mitochondria. Several reports support this possibility. Boime et al. have shown that LPC inhibits mitochondrial function during ischemia in the liver, and Wetter et al. have reported that LPC uncouples oxidative phosphorylation in rat liver mitochondria. In hearts, Ver Donck et al. have demonstrated that LPC produces Ca2+-overload and changes mitochondrial ultrastructure in isolated cardiac myocytes. Our recent study has also revealed that LPC inhibits respiratory function in rat cardiac mitochondria. These data suggest that LPC plays a role as a metabolic inhibitor of oxidative phosphorylation in mitochondria. These facts explain the reason why LPC decreases the tissue levels of ATP and CrP and increases the tissue level of lactate in isolated working rat hearts.

**Why does exogenous LPC accumulate FFA in the tissue?:** When the ATP level is low, fatty acyl CoA synthetase is inhibited as described before, and therefore, reacylation of LPC is also inhibited. It has been reported that LPC increases [Ca2+]i. When [Ca2+]i is increased, PLA2 is activated to release long-chain fatty acid that has been bound to the second position of the glycerol backbone of membrane-phospholipids. This is a possible mechanism for accumulation of FFA induced by exogenous LPC. In addition, LPC at low concentrations can directly increase the PLA2 activity. It is reasonable then to assume that LPC can be newly produced in the myocardium when exogenous LPC is applied to the heart. This means that exogenous LPC can accelerate the production of endogenous LPC, and therefore the deleterious effect of LPC continues for a long time because of LPC-induced LPC production. We think that this vicious circle of LPC production is responsible for the myocardial damage induced by ischemia/reperfusion.

**Ca2+-overload induced by LPC in isolated cardiac myocytes:** It has been demonstrated that LPC produces Ca2+-overload in isolated cardiac myocytes. If LPC opens the voltage-dependent Ca2+ channel, the mechanism of LPC-induced [Ca2+]i increase can be easily understood. However, the increase in [Ca2+]i was not inhibited by Ca2+ channel blockers, indicating that the role of Ca2+ entry via the voltage-dependent Ca2+ channel in the LPC-induced [Ca2+]i increase is negligible. Our data with Ca2+ current also indicate that exogenous LPC does not increase the voltage-dependent Ca2+ current, but it does...
inhibit the current. If the voltage-dependent Ca\(^{2+}\) channel is not related to the increase in [Ca\(^{2+}\)], how does LPC increase [Ca\(^{2+}\)]? Although the exact mechanisms of the Ca\(^{2+}\)-overload induced by LPC are not fully clarified, several mechanisms have been proposed. One is that of Ca\(^{2+}\)-overload via Na\(^+\)/Ca\(^{2+}\) exchange after accumulation of intracellular Na\(^+\). It has been demonstrated that LPC inhibits myocardial Na\(^+\), K\(^+\)-ATPase, and that LPC causes long lasting bursts of Na\(^+\) influx because of prolongation of the inactivation process of the Na\(^+\) channel. It is possible that LPC first increases the intracellular Na\(^+\) concentration in cardiac myocytes because of inhibition of Na\(^+\)-K\(^+\) ATPase and the increased burst of the Na\(^+\) currents, and then produces Ca\(^{2+}\)-overload via the Na\(^+\)/Ca\(^{2+}\) exchange mechanism. The second possible mechanism is that LPC directly increases sarcolemmal permeability to Ca\(^{2+}\). Our study has revealed that LPC increases non-selective cation current including the Na\(^+\), K\(^+\) and Ca\(^{2+}\) currents, but it does not increase the Cl\(^-\) current in guinea-pig ventricular myocytes. The increase in the permeability to Ca\(^{2+}\) induced by LPC is lower than that to Na\(^+\) or

**Figure 5.** Schematic overview of the presumed mechanisms of Ca\(^{2+}\)-overload induced by exogenous LPC in isolated cardiac myocytes. LPC may increase directly [Ca\(^{2+}\)], via opening of non-selective cation channel (or pore). Alternatively, LPC may increase indirectly [Ca\(^{2+}\)], via the Na\(^+\)/Ca\(^{2+}\) exchange system after accumulation of [Na\(^+\)], which is caused by (1) inhibition of Na\(^+\)-K\(^+\) ATPase, (2) modification of the voltage-dependent Na\(^+\) channel, and/or (3) Na\(^+\)-entry via the non-selective cation channel (or pore). Because PLA\(_2\) is activated by an increase in [Ca\(^{2+}\)], it is possible that LPC itself has an ability to produce another LPC (a vicious circle of accumulation of LPC). This accelerates the increase in [Ca\(^{2+}\)].
K, but the speed of increase in [Ca\textsuperscript{2+}]\textsubscript{i} induced by LPC is estimated to be about 4 mM Ca\textsuperscript{2+} per second in the guinea-pig cardiac myocyte.\textsuperscript{18} This increase in the [Ca\textsuperscript{2+}]\textsubscript{i} induced by LPC is considered to be enough to cause myocardial cell damage. Nevertheless, it is unknown whether the LPC-induced increase in non-selective cation current is due to activation of some channel or direct effect on the membrane lipids. Because of the amphiphilic property of LPC, it is possible to assume that LPC makes a pore on the cell membrane through which ions can pass, leading to an increase in membrane permeability.\textsuperscript{28}

Figure 5 summarizes the possible mechanisms of Ca\textsuperscript{2+}-overload induced by LPC. LPC may directly increase [Ca\textsuperscript{2+}]\textsubscript{i} via opening of the non-selective cation channel (or pore?), or indirectly increase [Ca\textsuperscript{2+}]\textsubscript{i} via Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange system after increase in [Na\textsuperscript{+}]\textsubscript{i}, which has been caused by inhibition of the Na\textsuperscript{+}-K\textsuperscript{+} ATPase, modification of the voltage-dependent Na\textsuperscript{+} channel, and/or Na\textsuperscript{+} entry via the non-selective cation channel (or pore?). The effect of LPC on the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange system, however, remains to be elucidated. It is suggested that Ca\textsuperscript{2+} release induced by LPC from intracellular Ca\textsuperscript{2+} stores, such as sarcoplasmic reticulum (SR), is related to the LPC-induced increase in [Ca\textsuperscript{2+}]\textsubscript{i}, because simultaneous treatment with ryanodine and thapsigargin (that inhibit the release of Ca\textsuperscript{2+} from SR) partially inhibits the degree of LPC-induced increase in [Ca\textsuperscript{2+}]\textsubscript{i}.\textsuperscript{29} Furthermore, it is possible to assume that a vicious circle of accumulation of LPC accelerates the increase in [Ca\textsuperscript{2+}]\textsubscript{i}, because manoalide, a PLA2 inhibitor, partially inhibits the degree of LPC-induced increase in [Ca\textsuperscript{2+}]\textsubscript{i}.\textsuperscript{29}

**LPC may potentiate ischemic damage:** Although there are some reports that LPC that has been accumulated in ischemic hearts is not responsible for both contractile dysfunction\textsuperscript{40} and Ca\textsuperscript{2+}-overload through Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange,\textsuperscript{31} LPC may potentiate the ischemia/reperfusion damage for the following reasons. Sedlis et al.\textsuperscript{32} reported that the depressant effect of LPC on contractile function is enhanced by acidosis and free radicals, both of which are produced during myocardial ischemia and reperfusion.

**LPC may activate protein kinase C in the heart:** Several studies suggest that LPC activates protein kinase C in the brain,\textsuperscript{33,34} T-lymphocytes\textsuperscript{35} and endothelial cells,\textsuperscript{36} and that LPC is involved in the signal transduction in these cells.\textsuperscript{33-35} In the vascular system, LPC that is contained in the oxidized low-density lipoprotein may play an important role in atherogenesis via activation of protein kinase C.\textsuperscript{36-39} In the heart, however, it is uncertain whether LPC actually activates protein kinase C or not. If LPC activates protein kinase C in the heart, it may affect signal transduction in the cardiac cells including slow response such as ventricular remodeling after myocardial infarction. It is also possible that protein kinase C is involved in the quick response in the myocardium; Ikeda et al.\textsuperscript{40} suggested that activation of protein kinase C accelerates hypoxic myocardial
injury by stimulating Na\(^+\)/H\(^+\) exchange, leading to Ca\(^{2+}\)-overload. Thus, there is a possibility that LPC potentiates the ischemic injury by activation of protein kinase C, although this possibility needs to be proved.

**Effects of Drugs on Cardiac Damage Induced by LPC**

The foregoing discussion points out that LPC accumulates during ischemia and reperfusion and produces ischemia/reperfusion-like damage. In addition, LPC produces new LPC in a way of establishing a vicious circle. We can speculate then that a drug which counteracts the cardiac effect of LPC may protect the heart against ischemia/reperfusion damage. Therefore, we tried to examine whether there are any drugs which can counteract the effect of LPC to produce mechanical and metabolic derangements, and also counteract the effect of LPC to produce Ca\(^{2+}\)-overload. The results will be described below.

**Anti-LPC effects of d-propranolol and dilazep:** Usually anti-ischemic drugs are classified into three groups; nitrates, \(\beta\)-adrenoceptor antagonists and Ca\(^{2+}\) channel blockers. We studied the effects of propranolol and diltiazem in isolated working rat hearts, and found that both propranolol and diltiazem are effective in attenuating ischemic damage. Surprisingly, we also found that d-propranolol (an optical isomer of propranolol having less \(\beta\)-adrenoceptor antagonistic action than propranolol) has anti-ischemic action to a similar extent to that of propranolol,\(^{41}\) and l-cis-diltiazem (an optical isomer of diltiazem having less Ca\(^{2+}\) channel antagonistic action than diltiazem) has anti-ischemic action to a similar extent to that of diltiazem.\(^{42}\) We also examined the anti-ischemic action of dilazep, which is not classified as a \(\beta\)-adrenoceptor antagonist or Ca\(^{2+}\) channel blocker, and found that dilazep also has anti-ischemic action.\(^{43}\)

We therefore examined the effects of dilazep and d-propranolol on the LPC-induced mechanical and metabolic changes in the heart. The results of our experiments using the perfused working rat heart have revealed that both dilazep and d-propranolol inhibit the mechanical and metabolic derangements induced by LPC.\(^{19}\) Because both dilazep and d-propranolol possess a Na\(^{+}\) channel blocking action,\(^{45}\) we thought that the mechanism of the inhibitory effect of these drugs on the LPC-induced derangements was the Na\(^{+}\) channel blocking action. However, lidocaine, a local anesthetic which blocks the voltage-dependent Na\(^{+}\) channel, did not inhibit the LPC-induced derangements.\(^{19,46}\) Similar results were obtained in experiments using isolated cardiac myocytes; dilazep and d-propranolol inhibited the Ca\(^{2+}\)-overload induced by LPC, but tetrodotoxin (a selective voltage-dependent Na\(^{+}\) channel blocker) did not (Figure 6). These data indicate that dilazep and d-propranolol possess both anti-ischemic and anti-LPC actions. We think that their anti-ischemic action may be due to their anti-LPC
Figure 6. Effects of dilazep, d-propranolol and tetrodotoxin (TTX) on the intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) in isolated cardiac myocytes. Note that application of LPC increased [Ca\(^{2+}\)]\(_i\) rapidly and markedly. Simultaneous application of TTX with LPC did not attenuate the effect of LPC, whereas simultaneous application of d-propranolol or dilazep with LPC attenuated the effect of LPC.

action. Nevertheless, the exact mechanism of anti-LPC action of these drugs remains unclear.

**Effects of K-7259 and various β-adrenoceptor antagonists:** A possible mechanism of the action of dilazep is potentiation of the cardiac action of adenosine, because dilazep has been reported to potentiate the cardiovascular action of adenosine. Recently, we found that K-7259, which is a derivative of dilazep having less potentiating action on the adenosine-mediated effects, attenuates the ischemia/reperfusion-induced cardiac damage. In addition, K-7259 attenuates the H\(_2\)O\(_2\)-induced cardiac mechanical dysfunction and H\(_2\)O\(_2\)-induced intracellular Ca\(^{2+}\)-overload. The effect of K-7259 on the LPC-induced cardiac damage is under study.

Another point that should be noted is the action of β-adrenoceptor antagonists on the LPC-induced Ca\(^{2+}\)-overload. We studied the effects of various β-adrenoceptor antagonists on the LPC-induced Ca\(^{2+}\)-overload in rat ventricular myocytes, and found that l-propranolol, d-propranolol, and l- or d-penbutolol had an anti-LPC effect, whereas pindolol, timolol, acebutolol, practolol, and atenolol did not, suggesting that β-adrenoceptor antagonistic effect does not protect the cardiac cells from the LPC-induced Ca\(^{2+}\)-overload.

**A possible approach to the development of new anti-ischemic drugs:** It is possible that drugs possessing the anti-LPC effect can inhibit or decrease the deleterious effect of LPC, leading to protection of ischemic damage. Table II
summarizes the effects of various drugs we examined in terms of their anti-LPC effect, voltage-dependent Na⁺-channel blocking action and lipophilicity. Lipophilicity is expressed as a log octanol/water coefficient. It is suggested from Table II that drugs possessing both voltage-dependent Na⁺-channel blocking action and high lipophilicity are necessary to inhibit the effect of LPC. This is a new approach to the development of new drugs possessing an anti-LPC effect, and this new approach may lead to the development of new anti-ischemic drugs.

In order to develop drugs possessing an anti-LPC effect, we must know the exact mechanisms of the effect of LPC and the exact role of LPC in ischemic damage. At present, however, our knowledge is still limited. Further studies are necessary to clarify the exact mechanisms of the effect of LPC and the role of LPC in ischemic damage.

**Conclusion:** Evidence has indicated that LPC that accumulates in the ischemic myocardium initiates or potentiates ischemic damage. Development of drugs which can inhibit or attenuate the deleterious effect of LPC on the heart would be useful to find a more effective new drug that protects the heart against ischemic injury.

Because LPC possesses multiple effects, it may be difficult to find a drug which inhibits all the deleterious effects of LPC. Nevertheless, combination of some drugs, each of which inhibits different effects of LPC would have beneficial effects on the ischemia-reperfused heart.
REFERENCES


46. Chen M, Hashizume H, Abiko Y. Effects of ß-adrenoceptor antagonists on Ca2+-overload induced by


