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Mexiletine and lidocaine reduce post-ischemic functional and biochemical dysfunction of perfused hearts ☆

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Abstract

The present study was undertaken to determine whether class Ib antiarrhythmic agents, mexiletine and lidocaine, exert beneficial effects on ischemia/reperfusion-induced cardiac contractile dysfunction. Isolated rat hearts were subjected to 35-min global ischemia, followed by 60-min reperfusion and the functional and metabolic alterations were examined with and without mexiletine or lidocaine treatment. Ischemia/reperfusion resulted in a lack of recovery of contractile function, a sustained rise in left ventricular end-diastolic pressure and increased coronary perfusion pressure of the perfused heart during reperfusion. Contractile dysfunction was associated with increases in tissue Na^+ and Ca^{2+} levels, decreases in K^+ and Mg^{2+} levels, and release of creatine kinase and purine nucleosides and bases (ATP metabolites) from the heart. Treatment of the perfused heart with either 10–100 μM of either mexiletine or lidocaine during pre-ischemia resulted in an enhancement of post-ischemic contractile recovery, a suppression of changes in tissue Na^+, K^+, Ca^{2+} and Mg^{2+} contents and an attenuation of the release of creatine kinase and ATP metabolites in an almost concentration-dependent manner. Tissue sodium accumulation was observed at the end of ischemia, which was also attenuated by pretreatment with these agents. The prevention of Na^+ overload and accompanying Ca^{2+} overload in cardiac cells may be the mechanism underlying the improvement of post-ischemic contractile function of perfused hearts by these agents.

Keywords: Ca^{2+} overload; Ischemia/reperfusion; Lidocaine; Mexiletine; Na^+ overload

1. Introduction

Mexiletine is known to exert antiarrhythmic effects in experimental animals and patients with arrhythmias (see Monk and Brogden, 1990), and is classified as a class Ib antiarrhythmic agent. Electrophysiological study has shown that this agent, like lidocaine, enhances the threshold of excitability, decreases the conduction velocity, shortens the effective refractory period and action potential duration, increases the ratio of effective refractory period to action potential duration, and blocks myocardial sodium currents (Chew et al., 1979; Hering et al., 1983; Woosley et al., 1984). Several reports have shown that mexiletine is effective to suppress ischemia-induced arrhythmias, which may obviously be beneficial for ischemic cardiac function (Amerini et al., 1985; Duff and Gault, 1986). In addition to arrhythmogenesis, ischemia/reperfusion also induces a prolonged contractile failure depending upon the duration of ischemic periods in animals (Braunwald and Kloner, 1982; Bolli et al., 1988). Little information is, however, available in the literature concerning the effects of mexiletine on contractile dysfunction induced by ischemia followed by reperfusion.

In previous studies we demonstrated that several antiarrhythmic agents improved ischemia/reperfusion-induced contractile dysfunction of perfused rat hearts (Liu et al., 1993a,b,c). In those studies, we postulated that the mechanism underlying the beneficial effect of the antiarrhythmic agents on ischemic/reperfused injury was attributable to prevention of Na^+ overload followed by Ca^{2+} overload in cardiac cells. The purpose of the present study was to determine whether mexiletine, which exerts a Na^+ channel blocking ac-

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tion, has protective effects on ischemia/reperfusion-induced cardiac contractile dysfunction which is accompanied by tissue Na^+ accumulation. The effects of lidocaine, a typical class Ib type antiarrhythmic agent, were also examined for the purpose of comparison.

2. Materials and methods

Male Wistar rats, weighing 270–300 g, were used in the present study. The animals were conditioned at 23 ± 1°C with a constant humidity of 55 ± 5%, a cycle of 12-h light and 12-h dark, and freely accessed food and tap water, according to the Guideline of Experimental Animal Care issued from the Japanese Prime Minister's Office.

2.1. Perfusion of hearts

The animals were lightly anesthetized with ether, and stunned by a blow to the head. The hearts were rapidly isolated and placed in the glass organ bath of a Langendorff apparatus and perfused at 37°C with a constant flow rate (9 ml/min) of Krebs-Henseleit solution of the following composition (mM): NaCl 120, KCl 4.8, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 1.25, $NaHCO_3$ 25 and glucose 11. The perfusion buffer was equilibrated with a gas mixture of 95% O_2 + 5% CO_2 (pO_2, > 600 mmHg). A latex balloon with uninflated diameter of 3.7 mm, connected to a pressure transducer (model TP-200T, Nihonkohden, Tokyo), was inserted into the left ventricular cavity through the mitral opening, and was secured with a ligature which included the left atrial remnants. Five mmHg of initial left ventricular end-diastolic pressure (LVEDP) was loaded. Perfusion pressure was monitored through a branch of an aortic cannula by means of an electronic manometer (model TP-400T, Nihonkohden, Tokyo) connected to a carrier amplifier (model AP-621G, Nihonkohden, Tokyo). Left ventricular developed pressure (LVDP), a measure of cardiac contractile force, was monitored by another electronic manometer and recorded with a thermal pen recorder (model WT-645G, Nihonkohden, Tokyo) throughout the experiment. The first derivative of the LVDP (left ventricular dP/dt) was also measured by means of a differentiator (model ED-601, Nihonkohden, Tokyo) connected to the carrier amplifier for LVDP. After 15-min equilibration, the heart was paced at 300 beats/min with an electrical stimulator via two silver electrodes directly attached to the heart and further equilibrated for 15 min. After equilibration was reached, the perfusion was stopped and the hearts were submerged in an organ bath which was filled with the Krebs-Henseleit solution as above except for the replacement of 11 mM glucose with 11 mM Tris/HCl. This solution was previously equilibrated with a gas mixture of 95% N_2 + 5% CO_2 (pO_2, < 10 mmHg), pH 7.4, and maintained at 37°C to prevent hypothermia-induced cardioprotection. The pH of both perfusing and bathing buffers was maintained between 7.40 to 7.42 throughout the experiment. After 35-min ischemia, the buffer in the organ bath was drained and the hearts were reperfused for 60 min at 37°C with normal Krebs-Henseleit solution saturated with a gas mixture of 95% O_2 + 5% CO_2 ($n = 10$). The hearts were paced throughout the experiment except for the first 15 min of reperfusion, to prevent contractile irregularities which might occur during this period. For the purpose of comparison, rat hearts were perfused for 95 min under normoxic conditions (normoxic group, $n = 6$).

Treatment of the perfused heart with different concentrations (10, 30 and 100 μM) of mexiletine (n = each 6) and lidocaine (n = each 5) was carried out by infusing these agents into the perfusing buffer for the last 3-min pre-ischemia. The agent was dissolved in a Krebs-Henseleit solution as above and infused through an injection port located just prior to the aortic cannula at a flow rate of 0.1 ml/min by a microtube pump (Terumo STC-523, Terumo Co., Tokyo). The agents were dissolved in physiological saline.

2.2. Measurement of tissue ion content

At an appropriate time in the experimental sequence (at the pre-ischemia, 35-min ischemia, or 60-min reperfusion), the perfusion of hearts was stopped and the vascular space of the heart was washed with 8 ml of a cold buffer containing 320 mM sucrose and 20 mM Tris/HCl, pH 7.4, via the aortic cannula. The myocardial ion content was measured according to the method described previously (Takeo et al., 1991). The wet myocardium was dried at 120°C for 48 h. After its dry weight was determined, the tissue was digested to evaporation at 180°C with concentrated HNO_3. The residue was reconstituted with 2.5 ml of 0.75 N HNO_3 and used for determination of tissue ion content with an atomic absorption spectrometer (model AA-680, Shimazu Seisakusho, Kyoto, Japan). For determination of Ca^{2+}, the reconstituting solution additionally contained 5 mM $LaCl_3$ and 0.05 N HCl. In another set of experiments, the myocardial ion content at 35-min ischemia was determined in the same manner.

2.3. Examination of perfusate

The perfusate from the heart was collected in a beaker cooled on ice during reperfusion. The creatine kinase activity of the perfusate was determined by the method of Bergmeyer et al. (1970). The release was estimated as the total creatine kinase activity of the effluent from the reperfused heart.

The perfusate was also used for determination of purine nucleosides and bases (ATP metabolites) by high-performance liquid chromatography (HPLC). The ATP metabolites were separated through a column of C_{18}-cellulose acetate (Cosmosil 5C18, Nakarai Tescque, Kyoto, Japan) with 4.6-mm diameter and 15-cm length, by elution with 0.25 M KH_2PO_4 containing 3.5% CH_3CN, pH 6.0, at a flow rate of 1 ml/min (model L-6000, Hitachi, Tokyo, Japan). UV absorbance of the eluate was monitored at 254 nm using a Hitachi UV-detector (model L-4000, Hitachi, Tokyo, Japan). The release of ATP metabolites was estimated as total amount of ATP metabolites of the effluent from the reperfused heart. The details of HPLC analysis were described previously (Takeo et al., 1991).

2.4. Statistics

The results are expressed as the means ± S.E.M. Statistical significance was evaluated using an analysis for trends (Williams multiple comparison) when the efficacy of agents was evaluated and Student's *t*-test when the two groups were tested. A confidence level of more than 95% was considered significant ($P < 0.05$).

3. Results

3.1. Cardiac function of the perfused heart

Changes in LVDP, LVEDP and coronary perfusion pressure of ischemic/reperfused hearts without (control) and with either mexiletine or lidocaine treatment are shown in Figs. 1–3, respectively. LVDPs of the hearts treated with 10, 30 and 100 μM mexiletine were 94 ± 2, 85 ± 4 and 35 ± 10% of initial and those with 10, 30 and 100 μM lidocaine, 95 ± 2, 86 ± 4 and 82 ± 2% of initial, respectively, at the end of pre-ischemia. Ischemia induced a rapid decline in LVDP to reach zero within 1.5 min of ischemia. Thereafter, no LVDP was generated during ischemia and reperfusion when the heart was untreated. In contrast, the LVDP recovered in a concentration-dependent manner after reperfusion when the heart was treated during pre-ischemia with 10–100 μM of either mexiletine or lidocaine. Similar changes were seen in left ventricular dP/dt of the untreated and treated hearts (data not shown).

LVEDP was increased approximately 15 min after the onset of ischemia, and reached peak levels of 64 + 7 mmHg at 20 min of ischemia. The LVEDP was further increased upon reperfusion, and this high level of LVEDP was sustained throughout reperfusion. Treatment with either 30 and 100 μM mexiletine, or 100 μM lidocaine attenuated the rise in LVEDP during reperfusion.

Coronary perfusion pressure was appreciably increased during treatment with lidocaine, but not mexiletine. Ischemia induced an immediate decline in the perfusion pressure of all hearts examined. The perfusion pressure of the untreated heart increased above baseline levels upon reperfusion, and this increased level was sustained throughout reperfusion. The increase in perfusion pressure during reperfusion was attenuated by treatment with either 10 or 100 μM mexiletine, whereas lidocaine treatment resulted in a marginal effect on coronary perfusion pressure during reperfusion.

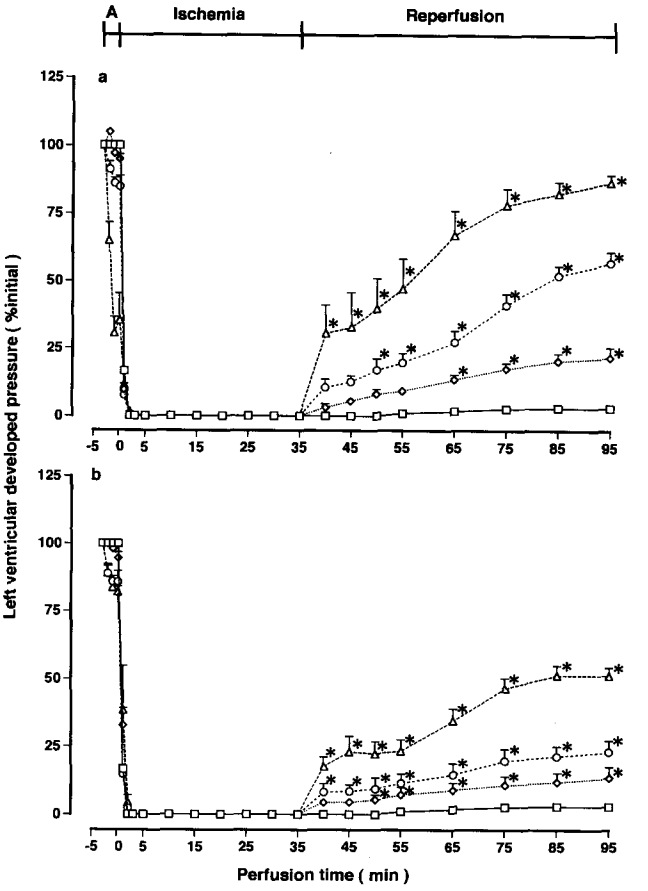

Fig. 1. Time course of changes in left ventricular developed pressure of the ischemic/reperfused heart without (□) and with different concentrations (10, ◇; 30, ○; and 100 μM, △) of either mexiletine (a, upper panel) or lidocaine (b, lower panel). Each value represents the mean ± S.E.M. of ten (untreated group), each six (mexiletine-treated) and each five (lidocaine-treated) experiments. Treatment with the agents was conducted during period 'A'. In the time course study, statistical differences between untreated and treated groups of the reperfused heart were evaluated. The standard errors of the symbols without any bar are within 1%. * Significantly different from untreated group ($P < 0.05$).

3.2. Determination of perfusate content

3.2.1. Release of creatine kinase

To determine the release of creatine kinase from perfused hearts, the perfusate was collected and its creatine kinase activity was measured (Fig. 4). During

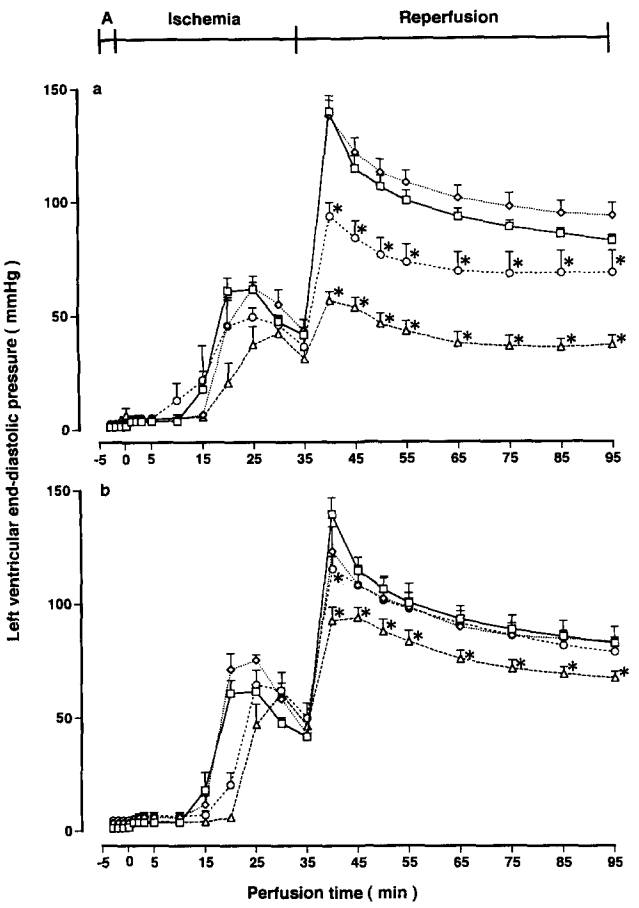

Fig. 2. Time course of changes in left ventricular end-diastolic pressure of the ischemic/reperfused heart without and with different concentrations of either mexiletine or lidocaine. Each value represents the mean ± S.E.M. Symbols and numbers of experiments and statistics are the same as those in Fig. 1.

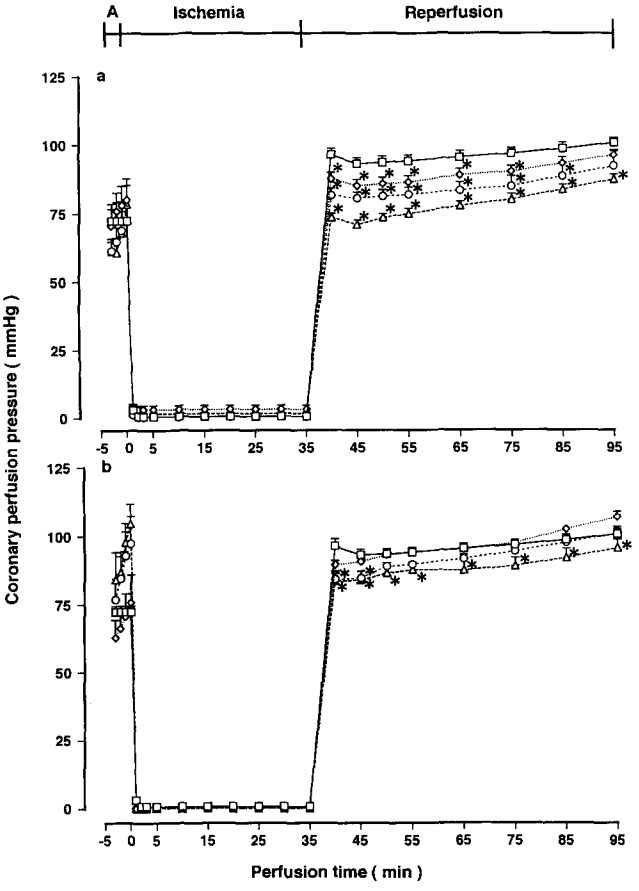

Fig. 3. Time course of changes in coronary perfusion pressure of the ischemic/reperfused heart without and with different concentrations (10, 30 and 100 μM) of either mexiletine or lidocaine. Each value represents the mean ± S.E.M. Symbols and numbers of experiments and statistics are the same as those in Fig. 1.

30-min pre-perfusion, creatine kinase activity in the perfusate was negligible (< 1 nmol NADPH/min per g wet tissue). There was a negligible amount of creatine kinase released from normoxic hearts throughout normoxic perfusion (< 2 nmol NADPH/min per g wet tissue). The release of creatine kinase increased markedly during reperfusion (157 ± 5 nmol NADPH/min per g wet tissue). Treatment of the perfused heart with mexiletine attenuated the release of creatine kinase during reperfusion in a concentration-dependent manner. Lidocaine also attenuated the release of creatine kinase significantly but to a lesser degree than mexiletine.

3.2.2. Release of ATP metabolites

Release of ATP metabolites during reperfusion was determined. The ATP metabolites released during reperfusion were mainly inosine, hypoxanthine, and adenosine. In the present study, the sum of these metabolites released during reperfusion was determined and used as a measure of the release of ATP

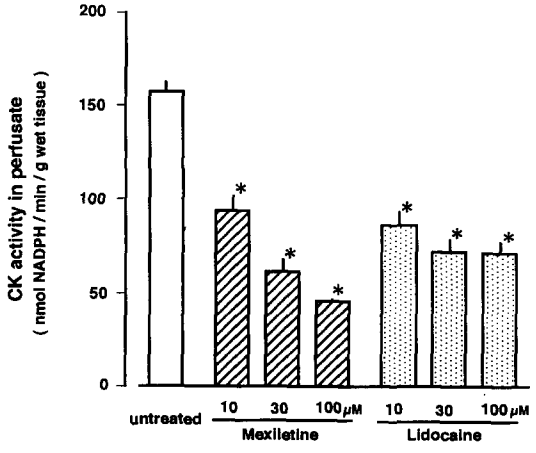

Fig. 4. Creatine kinase activity in perfusate eluted from untreated hearts (open column), and hearts treated with different concentrations (10, 30 and 100 μM) of either mexiletine (hatched column) or lidocaine (stippled column). Each value represents the mean ± S.E.M. of ten (untreated group), six (mexiletine-treated) and five (lidocaine-treated) experiments. * Significantly different from untreated group ($P < 0.05$).

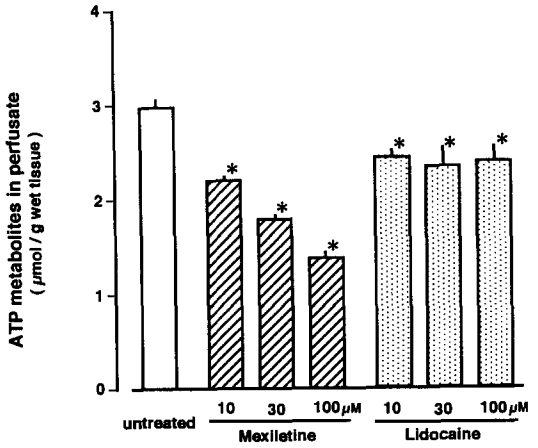

Fig. 5. ATP metabolites in perfusate eluted from untreated, and either mexiletine-or lidocaine-treated hearts. Each value represents the mean ± S.E.M. Symbols and numbers of experiments are the same as those in Fig. 4.

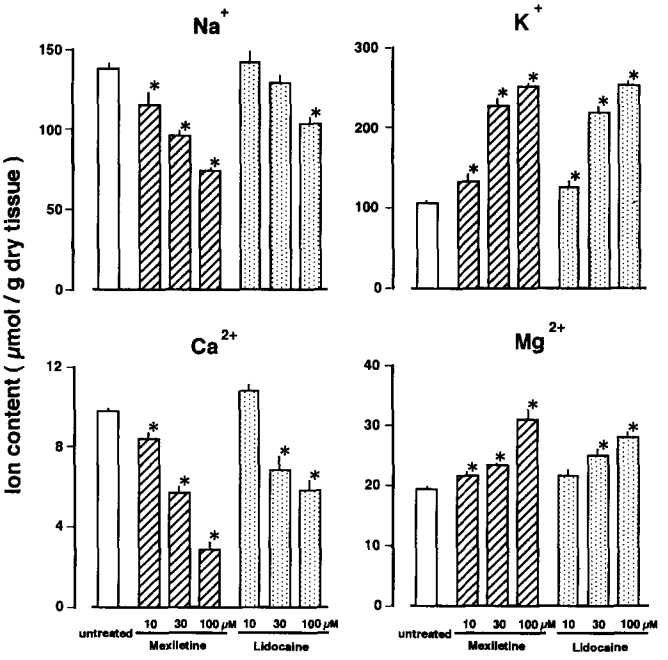

Fig. 6. Tissue Na^+, K^+, Ca^{2+} and Mg^{2+} contents of the ischemic/reperfused hearts and hearts untreated or treated with different concentrations (10, 30 and 100 μM) of either mexiletine or lidocaine and the normoxic heart at the end of reperfusion and normoxic perfusion. Each value represents the mean ± S.E.M. Symbols and numbers of experiments are the same as those in Fig. 4.

metabolites (Fig. 5). A minimal release of ATP metabolites was detected during pre-ischemia (< 0.1 μmol/g wet tissue). No appreciable release was observed from normoxic hearts throughout the normoxic perfusion (< 0.2 μmol/g wet tissue). The release of ATP metabolites was markedly increased during reperfusion (2.975 ± 0.089 μmol/g wet tissue). Treatment with 10–100 μM mexiletine resulted in a significant and concentration-dependent suppression of the release of ATP metabolites during reperfusion. Relatively minor inhibition of the release of ATP metabolites was detected when the hearts were treated with 10–100 μM lidocaine.

3.3. Tissue ion content

Tissue Na^+, K^+, Ca^{2+} and Mg^{2+} and water content of the perfused hearts without and with 10–100 μM of either mexiletine or lidocaine were determined, and the results are shown in Fig. 6. Treatment of the normoxic hearts with either 100 μM mexiletine or 100 μM lidocaine did not elicit any change in these ion contents, indicating that there was no change in tissue ion content during pretreatment of the pre-ischemic heart with mexiletine or lidocaine (data not shown). Significant increases in Na^+ and Ca^{2+}, and decreases in K^+ and Mg^{2+} contents were observed in ischemic/reperfused hearts at the end of reperfusion. Concentration-dependent preservation of myocardial Na^+, K^+, Ca^{2+} and Mg^{2+} levels was observed at the end of reperfusion when the hearts were pretreated with either mexiletine or lidocaine. The tissue water content of normoxic and ischemic/reperfused hearts was 77.0 ± 0.7 and 79.8 ± 0.7%, respectively. The tissue water content of the reperfused hearts was not altered by pretreatment with either mexiletine or lidocaine during pre-ischemia.

In another set of experiments, rat hearts were subjected to 35-min ischemia after no pretreatment or pretreatment with either 100 μM mexiletine or 100

Table 1
Tissue ion content of untreated, and mexiletine- or lidocaine-treated hearts at the end of ischemia

	Na^+	K^+	Ca^{2+}	Mg^{2+}	H_2O
Pre-ischemia	54.4 ± 4.1	349.1 ± 16.4	1.91 ± 0.15	36.7 ± 1.5	77.0 ± 0.4
Ischemia					
Untreated	123.2 ± 8.5 [a]	164.2 ± 18.9 [a]	2.44 ± 0.96	33.0 ± 4.6	82.8 ± 1.1 [a]
Mexiletine	99.4 ± 8.9 [b]	338.5 ± 15.2 [b]	1.90 ± 0.24	38.2 ± 1.2	78.0 ± 1.4 [b]
Lidocaine	107.0 ± 7.3 [b]	318.0 ± 15.1 [b]	2.00 ± 0.76	36.6 ± 1.9	78.3 ± 1.7 [b]

Values are expressed as μmol/g dry tissue for ions and % for water content. Each value represents the mean ± S.E.M. of six (pre-ischemia), six (untreated), four (mexiletine) and five (lidocaine) experiments. The hearts were not treated or treated with either 100 μM mexiletine or 100 μM lidocaine during the last 3 min of pre-ischemia. The sample at pre-ischemia was taken at 3 min before ischemia. [a] Significantly different from pre-ischemic group and [b] significantly different from untreated group ($P < 0.05$).

μM lidocaine to measure tissue ion levels after ischemia and the effects of mexiletine and lidocaine on the ion levels (Table 1). Ischemia caused a significant increase in Na^+ and decrease in K^+, but no appreciable changes in tissue Ca^{2+} and Mg^{2+} were observed. Pretreatment with either 100 μM mexiletine or 100 μM lidocaine resulted in a significant attenuation of changes in tissue Na^+ and K^+ contents at the end of ischemia. Tissue Ca^{2+} and Mg^{2+} contents of the ischemic heart were not altered regardless of no treatment or treatment with the agents. The tissue water content was increased after ischemia when the heart was untreated during pre-ischemia, which was slightly, but significantly attenuated by treatment with these agents.

4. Discussion

In the present study we observed an appreciable enhancement of post-ischemic contractile recovery of ischemic/reperfused hearts when they were treated during pre-ischemia with class Ib antiarrhythmic agents, mexiletine and lidocaine, at concentrations ranging from 10 to 100 μM. When the same drug concentration was used, mexiletine-treated hearts exhibited a better recovery of LVDP than lidocaine-treated hearts. As described in the Introduction, we had previously demonstrated that the post-ischemic contractile recovery of perfused rat hearts was also enhanced by treatment with class Ia and Ic type antiarrhythmic agents including disopyramide, propafenone, quinidine, flecainide and pilsicainide (Liu et al., 1993a,b,c). Since all of these agents, including mexiletine and lidocaine, are considered to block Na^+ channels, it may be concluded that antiarrhythmic agents which have a Na^+ channel blocking action are capable of improving ischemia/reperfusion-induced cardiac contractile dysfunction to an appreciable degree.

Ischemia rapidly produces acidosis in cardiac cells (Poole-Wilson, 1978; Couper et al., 1984; Lazdunski et al., 1985), possibly due to accumulation of inorganic phosphate produced by ATP breakdown, and/or lactate and hydrogen produced by anaerobic metabolism (Neely and Morgan, 1974; Vary et al., 1981; Dennis et al. 1991). This may lead to stimulation of Na^+/H^+ exchange, resulting in an excessive Na^+ overload in ischemic or anoxic cardiac cells (Frelin et al., 1984; Lazdunski et al., 1985; Schömig et al., 1988; Tani and Neely, 1989; Meng and Pierce, 1991; Van Echteld et al., 1991). Ischemia-induced Na^+ overload in cardiac cells may enhance Ca^{2+} overload in the cell by stimulating the Na^+/Ca^{2+} exchange mechanism (Tani and Neely, 1989), or by increasing cell membrane permeability (Crake and Poole-Wilson, 1990), when oxygen is replenished. The resulting increase in intracellular Ca^{2+} may exert deleterious effects on the mechanical function and biochemical activities of cardiac cells (Crake and Poole-Wilson, 1990; Chien et al., 1979; Das et al., 1986; Reddy et al., 1974). These sequences may eventually lead to cardiac contractile dysfunction. In the present study, we examined changes in tissue ion content of the perfused heart at the end of ischemia as well as after reperfusion, and found that ischemia per se substantially increased tissue Na^+ and decreased tissue K^+ without changes in tissue Ca^{2+} and Mg^{2+}. The results suggest that the ischemic insult in the present study produced ionic disturbance in a manner selective for Na^+ and K^+. Na^+/K^+ ATPase in cardiac cells functions in the presence of ATP. Due to a shortage of ATP, the function of the sodium pump in ischemic cardiac cells would be limited or inhibited. Such inhibition of sodium pump activity may cause an increase in intracellular Na^+ and a decrease in intracellular K^+ in the ischemic myocardium. This is consistent with the findings of other investigators that sarcolemmal Na^+/K^+ ATPase in the ischemic or hypoxic myocardium is inhibited (Bersohn et al., 1982; Daly et al., 1984). Na^+ accumulation and K^+ loss in the myocardium as observed in the present study may result from stimulation of Na^+/H^+ exchange and inhibition of the Na^+/K^+ pump. Treatment with mexiletine and lidocaine resulted in inhibition of ischemia-induced Na^+ overload and K^+ loss in the myocardium, suggesting that these agents prevent ischemia-induced ionic disturbance in cardiac cells.

Reperfusion as employed in the present study caused a further increase in tissue Na^+ and a decrease in tissue K^+ accompanied by a significant increase in tissue Ca^{2+} and a decrease in tissue Mg^{2+}, that is, a profound change in all tissue ion contents examined. This suggests that reperfusion not only causes Na^+ overload and subsequent Ca^{2+} overload, but also induces a disruption of cell membrane integrity or a non-specific increase in cell membrane permeability to ions across the sarcolemma. A reperfusion-induced increase in Ca^{2+} permeability which is independent of Na^+/Ca^{2+} exchange mechanism has been postulated to occur in hypoxic/reoxygenated rabbit hearts (Crake and Poole-Wilson, 1990). In the present study ischemia/reperfusion-induced tissue Na^+ and Ca^{2+} accumulation was diminished by treatment with these two agents during pre-ischemia. Since these two agents were found to attenuate reperfusion-induced K^+ and Mg^{2+} loss, it is likely that these agents block the relatively non-selective ionic flux induced by reperfusion as well.

The enhancement of post-ischemic contractile recovery in the present study was associated with suppression of the release of creatine kinase and the ATP metabolites from the reperfused heart. Release of creatine kinase from reperfused hearts, a loss of the macromolecular cytosolic constituent, is thought to be

an indication of disruption of cardiac cell membrane and/or an increase in cell membrane permeability (Hearse and Humphrey, 1975; Ganote and Kaltenbach, 1979). Thus, it represents a non-specific change in membrane permeability across the sarcolemma. Treatment of pre-ischemic hearts with mexiletine or lidocaine resulted in a profound suppression of the loss of creatine kinase from the reperfused heart, suggesting that these agents are capable of inhibiting cardiac cell necrosis and/or detrimental changes in cell membrane permeability.

From the results in the current study we have postulated that class Ib antiarrhythmic agents, mexiletine and lidocaine, are capable of exerting beneficial effects on contractile function of ischemic/reperfused hearts. Since the inhibition of transmembrane fluxes of ions, macromolecules and substrates was detected, it could be concluded that protection of membrane integrity by these agents, particularly prevention of ischemia/reperfusion-induced Na^+ overload and subsequent Ca^{2+} overload, plays a role in the enhancement of post-ischemic contractile recovery of the perfused heart.

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