Ranolazine Attenuates Palmitoyl-L-carnitine-induced Mechanical and Metabolic Derangement in the Isolated, Perfused Rat Heart

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Abstract

The effect of ranolazine, a novel anti-ischaemic drug that stimulates the activity of pyruvate dehydrogenase, on palmitoyl-L-carnitine-induced mechanical dysfunction and metabolic derangement in isolated perfused rat hearts has been studied and compared with the effect of dichloroacetate, an activator of pyruvate dehydrogenase.

Rat hearts paced electrically were perfused aerobically at constant flow by the Langendorff technique. Palmitoyl-L-carnitine ($4\,\mu$M) increased left ventricular end-diastolic pressure and reduced left ventricular developed pressure (i.e. induced mechanical dysfunction); it also reduced tissue levels of adenosine triphosphate and increased tissue levels of adenosine monophosphate (i.e. induced metabolic derangement). These functional and metabolic alterations induced by palmitoyl-L-carnitine were attenuated by ranolazine (5, 10, and $20\,\mu$M) in a concentration-dependent manner. In contrast, dichloroacetate (1 and 10 mM) did not attenuate palmitoyl-L-carnitine-induced mechanical and metabolic derangement. In the normal (palmitoyl-L-carnitine-untreated) heart, however, ranolazine did not modify mechanical function and energy metabolism.

These results suggest that ranolazine attenuates palmitoyl-L-carnitine-induced mechanical and metabolic derangement in the rat heart, and that the beneficial action of ranolazine is not because of the energy-sparing effect or activation of pyruvate dehydrogenase.

It is generally accepted that the primary mechanism of action of anti-anginal drugs is improvement of myocardial oxygen balance between supply and demand either by increasing coronary flow or by reducing cardiac mechanical function, or both. These drugs exert their anti-anginal action via changes in haemodynamics. Anti-anginal drugs include nitrates, β-adrenoceptor antagonists, and Ca^{2+}-channel blockers, all of which have been used widely for treatment of patients with ischaemic heart disease.

Ranolazine [($\pm$)-*N*-(2,6 - dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine acetamide] has recently been shown to attenuate ischaemic derangement both in-vivo (Allely et al 1987; Allely & Alps 1990) and in-vitro (Clarke et al 1993; Gralinski et al 1994; McCormack et al 1996) in animal models. Clinical findings suggest that ranolazine is useful in angina pectoris therapy (Jain et al 1990; Cocco et al 1992).

Interestingly, the anti-ischaemic (Clarke et al 1993; Gralinski et al 1994; McCormack et al 1996) and anti-anginal (Jain et al 1990; Cocco et al 1992) action of ranolazine has no detectable effect on haemodynamics, and the mechanism of anti-ischaemic (and anti-anginal) action of ranolazine might, therefore, differ from that of nitrates, β-adrenoceptor antagonists, and Ca^{2+}-channel blockers (Hara et al 1999). McCormack et al (1996) showed that the cardioprotective action of ranolazine might, at least in part, be stimulation of carbohydrate oxidation by activation of pyruvate dehydrogenase, which regulates entry of pyruvate into the tricarboxylic acid cycle. Matsumura et al (1998) found that ranolazine attenuated the mechanical dysfunction and metabolic derangement induced by exogenous hydrogen peroxide. The inhibitive action of ranolazine on the effect of hydrogen peroxide might also contribute to its protection of the myocardium against ischaemia–reperfusion damage, in which reactive oxygen species are involved, although the mechanism of the anti-ischaemic effect of ranolazine is not fully understood.

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Long chain acylcarnitines, for example palmitoyl-L-carnitine, have been shown to promote ischaemia–reperfusion damage in the heart (Corr et al 1987, 1989; DaTorre et al 1991; Yamada et al 1994). During ischaemia myocardial levels of long-chain acylcarnitines increase markedly because of inhibition of mitochondrial β-oxidation of free fatty acids (Corr et al 1987; DaTorre et al 1991). Long-chain acylcarnitines accumulating in the tissues are preferentially incorporated into the phospholipid bilayers of the sarcolemmal membrane and cause myocardial derangement, including mechanical dysfunction and reduced levels of high-energy phosphates (Arakawa et al 1997; Hara et al 1997; Xiao et al 1997); inhibitors of carnitine acyl-transferase I reduce ischaemia-induced mechanical and metabolic derangement and tissue accumulation of long-chain acylcarnitines in the heart, both in-situ (Corr et al 1989) and in-vitro (Yamada et al 1994). It is, nevertheless, unclear whether ranolazine attenuates the myocardial derangement induced by palmitoyl-L-carnitine.

This study was conducted to investigate the effects of ranolazine on myocardial mechanical and metabolic derangement induced by exogenous palmitoyl-L-carnitine in the isolated perfused rat heart, and to compare the effects of ranolazine with those of dichloroacetate, an activator of pyruvate dehydrogenase (Stacpoole 1989; McVeigh & Lopaschuk 1990; Clarke et al 1996).

Materials and Methods

Drugs
Ranolazine hydrochloride (Kissei Pharmaceutical, Nagano, Japan), sodium dichloroacetate (Tokyo Kasei, Tokyo, Japan), and palmitoyl-L-carnitine (Sigma, St Louis, MO) were dissolved in Krebs-Henseleit bicarbonate (KHB) buffer. Reagents and enzymes used for biochemical analysis were purchased from Sigma.

Heart perfusion
This study was approved by the Animal Experiment Committee of Asahikawa Medical College. Male Sprague–Dawley rats (9–10 weeks; Sankyo Labo Service Corporation, Sapporo, Japan) were anaesthetized by intraperitoneal (i.p.) administration of sodium pentobarbital ($50 \, \text{mg kg}^{-1}$) 20 min after injection of heparin ($1000 \, \text{U kg}^{-1}$, i.p.). After thoracotomy, the hearts were rapidly removed, and retrograde perfusion, by the Langendorff technique, was started via a cannula inserted into the aorta.

The perfusion buffer was KHB buffer containing (mM): NaCl 118, KCl 4·7, KH_2PO_4 1·2, $MgSO_4$ 1·2, $CaCl_2$ 2·5, $NaHCO_3$ 25 and glucose 11 equilibrated with a gaseous mixture of 95% O_2 and 5% CO_2 and maintained at 37°C. The oxygen tension of the buffer, measured by means of a blood-gas analyser (Model 813, Instrumentation Laboratory, Lexington, MA), was $550 \, \text{mm Hg}$ (approx.) The hearts were initially perfused at a constant perfusion pressure of $80 \, \text{cm H}_2\text{O}$ for 10 min (approx.). Perfusion was then switched to constant-flow ($10 \, \text{mL min}^{-1}$) effected by means of a microtube pump (Eyela MP-A, Tokyo-Rikakikai Instruments, Tokyo, Japan); this flow rate was maintained constant throughout the experiment. During the study the heart rate was kept constant by pacing at $300 \, \text{beats min}^{-1}$ with an electronic stimulator (3F46, San-Ei Instruments, Tokyo, Japan). Rectangular 2-ms pulses at $6 \, \text{V}$ (approx. 3 times the threshold voltage) were applied to the left ventricle to pace the heart.

Left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), and left ventricular developed pressure (LVDP) were used as indicators of mechanical function. LVSP and LVEDP were determined from left ventricular pressure (LVP) curves recorded continuously during the course of the study; the LVDP value was calculated as LVSP minus LVEDP. For measurement of LVP, a saline-filled polyethylene cannula, connected to a pressure transducer, was inserted into the left ventricular cavity via the left atrium. Another pressure transducer was connected to the aortic cannula to record coronary perfusion pressure (CPP). Before the start of experiment the heart was left to stabilize for 20 min under constant flow perfusion.

Experimental protocol
The effects of ranolazine or dichloroacetate on mechanical function and energy metabolism were examined in both palmitoyl-L-carnitine-treated and palmitoyl-L-carnitine-untreated (normal) hearts. After the 20-min stabilization period ranolazine, dichloroacetate, or vehicle (KHB buffer) was infused, via an inflow tube connected to a side arm of the aortic cannula, for 40 min at a constant flow of $0·1 \, \text{mL min}^{-1}$. The final concentration of ranolazine in the perfusate was 5, 10, or 20 μM; that of dichloroacetate was 1 or 10 mM. In experiments with palmitoyl-L-carnitine-treated heart, palmitoyl-L-carritine was infused for 7 min through the inflow tube by means of a second infusion pump, starting 10 min after the start of infusion of ranolazine, dichloroacetate, or vehicle. The final concentration

of palmitoyl-L-carnitine was $4\,\mu$M. The experimental conditions and procedure for experiments with normal hearts were essentially the same as for the experiments on palmitoyl-L-carnitine-treated heart, except for infusion of KHB buffer instead of palmitoyl-L-carnitine solution. In each group, LVSP, LVEDP, and CPP were continuously recorded over a 40-min observation period. At the end of the observation period tissue levels of high-energy phosphates were measured after freezing the heart with freezing clamps previously chilled in liquid nitrogen.

Biochemical analysis

The frozen myocardial samples were stored in liquid nitrogen ($-196°$C) until biochemical analysis. Samples were pulverized in a mortar cooled with liquid nitrogen. The water content and dry weight of the tissue were measured by weighing a portion of the pulverized tissue powder and placing it in an oven overnight. The remaining tissue powder was used for determination of tissue levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and creatine phosphate (CrP). The pulverized tissue sample was extracted with 6% perchloric acid, the extract was centrifuged at $10\,000\,g$ for 10 min at $4°$C, and the supernatant was neutralized with 70% KOH and again centrifuged at $10\,000\,g$ for 10 min at $4°$C. The resulting solution was used for determination of ATP, ADP, AMP and CrP by means of a standard enzymatic procedure (Bergmeyer 1974).

Statistical analysis

All values are means $\pm$ s.e.m. When mechanical and metabolic data from vehicle-treated and drug-treated groups were compared, statistical analysis was performed by two-way analysis of variance then Dunnett's test for multiple comparison. When metabolic data from untreated rats were compared with those from rats treated with palmitoyl-L-carnitine, statistical analysis was performed by two-way analysis of variance then Dunnett's test. $P < 0.05$ was considered significant.

Results

Effects on mechanical function and coronary resistance

In the normal, untreated heart, ranolazine (5, 10, and $20\,\mu$M) and dichloroacetate (1 and $10\,$mM) had no effect on LVSP, LVEDP, LVDP, or CPP during the course of the study, suggesting that neither ranolazine nor dichloroacetate modifies the mechanical function or coronary resistance of the normal heart (data not shown). Figures 1 and 2 show the effects of ranolazine and dichloroacetate respectively, on palmitoyl-L-carnitine-induced changes in LVSP and LVEDP. Before the start of infusion of palmitoyl-L-carnitine (0, 5, and 10 min in Figures 1 and 2), there was no significant difference between values of LVSP and LVEDP among the vehicle, ranolazine, or dichloroacetate groups. In the vehicle group palmitoyl-L-carnitine reduced LVSP and increased LVEDP markedly. LVSP and LVEDP levels that had been modified by palmitoyl-L-carnitine did not return to initial values by the end of the experiment, suggesting that palmitoyl-L-carnitine induces long-lasting and irreversible mechanical dysfunction. Although neither ranolazine (5, 10, or $20\,\mu$M) nor dichloroacetate (1 or $10\,$mM) had a significant effect on the reduction in LVSP induced by palmitoyl-L-carnitine, ranola-
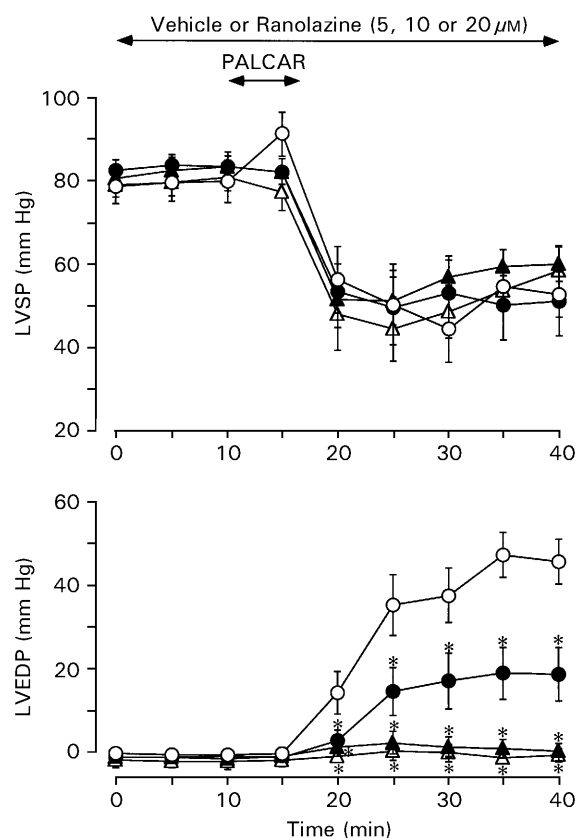

Figure 1. Effects of ranolazine on palmitoyl-L-carnitine-induced changes in mechanical function. Changes in left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP) for vehicle ($\bigcirc$) and ranolazine ($5\,\mu$M, $\bullet$; $10\,\mu$M, $\triangle$; $20\,\mu$M, $\blacktriangle$) groups are shown. The large arrow indicates the period of infusion of vehicle or ranolazine and the short arrow the period of infusion of palmitoyl-L-carnitine (PALCAR). Each value is the mean $\pm$ s.e.m. of results from 7 or 8 experiments. $*P < 0.05$ compared with vehicle.
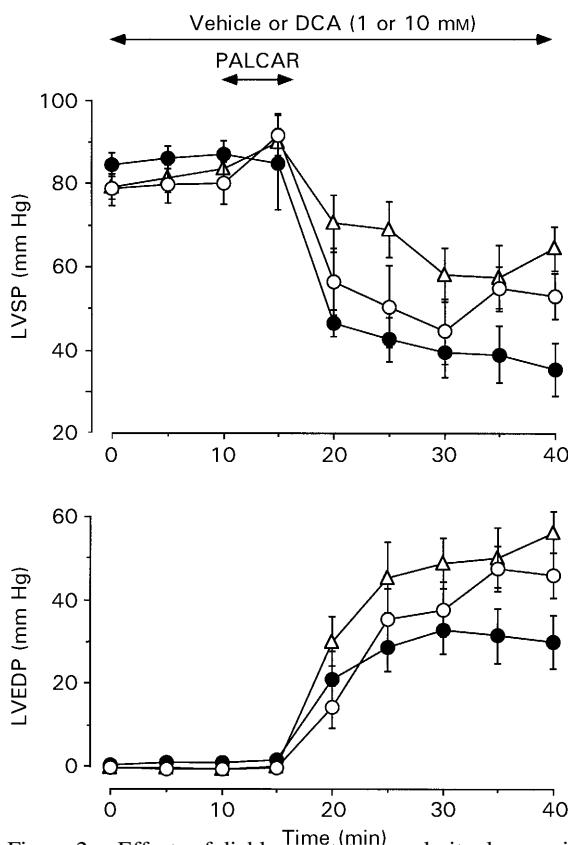
Figure 2. Effects of dichloroacetate on palmitoyl-L-carnitine-induced changes in mechanical function. Changes in left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP) for vehicle (○) and dichloroacetate (1 mM, ●; 10 mM, △) groups are shown. The large arrow indicates the period of infusion of vehicle or dichloroacetate (DCA) and the short arrow the period of infusion of palmitoyl-L-carnitine (PALCAR). Each value is the mean ± s.e.m. of results from 7 or 8 experiments. *$P < 0.05$ compared with vehicle.

zine (5, 10, or 20 μM) significantly attenuated the palmitoyl-L-carnitine-induced increase in LVEDP (Figure 1) whereas dichloroacetate (1 or 10 mM) did not (Figure 2).

Figure 3 shows the effects of ranolazine and dichloroacetate on palmitoyl-L-carnitine-induced changes in LVDP. Before the start of palmitoyl-L-carnitine infusion (0, 5, and 10 min in Figure 3), there was no significant difference between LVDP values among the vehicle, ranolazine or dichloroacetate groups. In the vehicle group, palmitoyl-L-carnitine markedly reduced LVDP, from 79 to 7 mm Hg (approx.). Ranolazine (5, 10, or 20 μM) attenuated the palmitoyl-L-carnitine-induced decrease in LVDP. At the end of the experiments (40 min in Figure 3), LVDP in the vehicle group was 7 mm Hg (approx.) whereas values for the 5-, 10- and 20-μM ranolazine groups were 32, 59, and 60 mm Hg (approx.), respectively. In contrast, dichloroacetate (1 and 10 mM) failed to attenuate the palmitoyl-L-carnitine-induced decrease in

LVDP. These results suggest that ranolazine could reduce palmitoyl-L-carnitine-induced mechanical dysfunction.

Figure 4 shows the effects of ranolazine and dichloroacetate on palmitoyl-L-carnitine-induced changes in CPP. Before infusion of palmitoyl-L-carnitine (0, 5, and 10 min in Figure 4), there was no significant difference between CPP values among the vehicle, ranolazine or dichloroacetate groups. Palmitoyl-L-carnitine caused a continuous and marked increase in CPP. Although the increase in CPP induced by palmitoyl-L-carnitine was attenuated by ranolazine (10 and 20 μM), neither the low (5 μM) concentration of ranolazine nor dichloroacetate (1 or 10 mM) attenuated the palmitoyl-L-carnitine-induced increase in CPP. These results suggest that ranolazine could lessen the
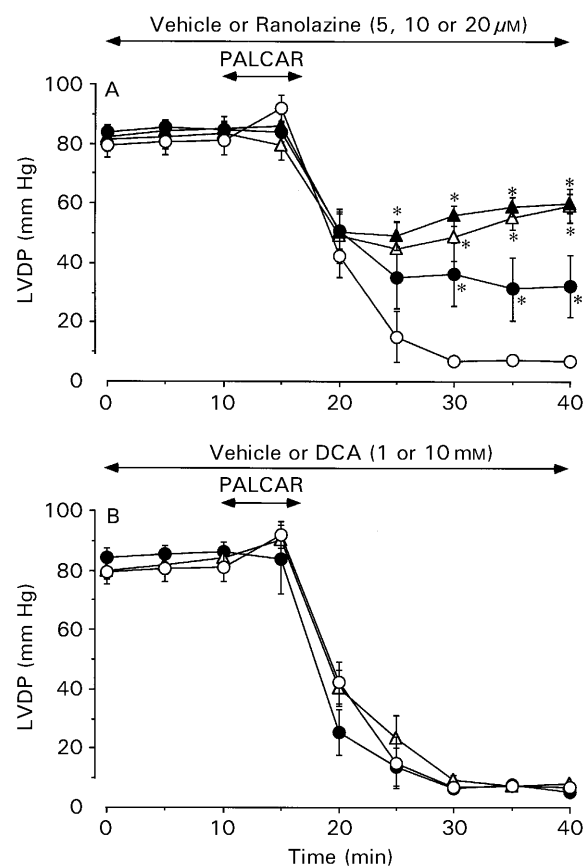

Figure 3. Effects of ranolazine (A) and dichloroacetate (B) on palmitoyl-L-carnitine-induced changes in left ventricular developed pressure (LVDP). Changes of LVDP for A. vehicle (○) and ranolazine (5 μM, ●; 10 μM, △ 20 μM, ▲) groups and B. vehicle (○) and dichloroacetate (1 mM, ●; 10 mM, △) groups are shown. The large arrows indicate the periods of infusion of vehicle or ranolazine (A) or dichloroacetate (B) and the short arrows the periods of infusion of palmitoyl-L-carnitine (A; PALCAR and B; DCA). Values were calculated from the values of left ventricular systolic pressure and left ventricular end-diastolic pressure in Figures 1 and 2 . Each value is the mean ± s.e.m. of results from 7 or 8 experiments. *$P < 0.05$ compared with vehicle.

palmitoyl-L-carnitine-induced increase in coronary resistance.

Effects on energy metabolism

Figure 5 depicts tissue levels of ATP, ADP, AMP, and CrP at the end of the experiment in normal and palmitoyl-L-carnitine-treated hearts. In normal hearts similar tissue levels of ATP, ADP, AMP, and CrP were measured for vehicle, ranolazine, and dichloroacetate groups, suggesting that neither ranolazine nor dichloroacetate modifies energy metabolism in the normal heart. In the vehicle group, palmitoyl-L-carnitine reduced tissue levels of ATP, ADP, and CrP and increased the level of AMP. ATP decreased from 17·7 to 6·1 μmol g^{-1} dry wt, ADP from 5·6 to 3·5 μmol g^{-1} dry wt and CrP from 19·2 to 10·6 μmol g^{-1} dry wt; AMP

increased from 1·3 to 3·2 μmol g^{-1} dry wt. The decrease in the tissue level of ATP induced by palmitoyl-L-carnitine was significantly attenuated by ranolazine (5, 10, and 20 μM). Ranolazine (20 μM) also attenuated palmitoyl-L-carnitine-induced changes in tissue levels of AMP and CrP. In contrast, dichloroacetate (1 and 10 mM) did not affect palmitoyl-L-carnitine-induced changes in tissue levels of ATP, ADP, AMP, or CrP. Thus, ranolazine attenuated palmitoyl-L-carnitine-induced metabolic derangement in the heart.
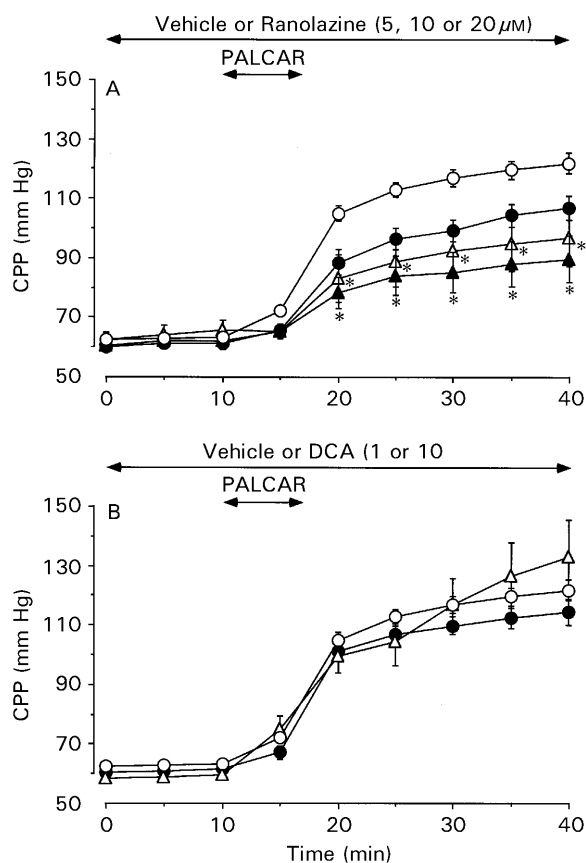

Figure 4. Effects of ranolazine (A) and dichloroacetate (B) on palmitoyl-L-carnitine-induced changes in coronary perfusion pressure (CPP). Changes in CPP for: A vehicle (○) and ranolazine (5 μM, ●; 10 μM, △; 20 μM, ▲) groups and B. vehicle (○) and dichloroacetate (1 mM, ●; 10 mM, △) groups are shown. The large arrows indicate the periods of infusion of vehicle or ranolazine (A) or dichloroacetate (B) and the short arrows the periods of infusion of palmitoyl-L-carnitine (A and B; PALCAR (B; DCA)). Hearts were those used to provide the data depicted in Figures 1–3. Each value is the mean ± s.e.m. of results from 6–8 experiments. *$P < 0.05$ compared with vehicle.
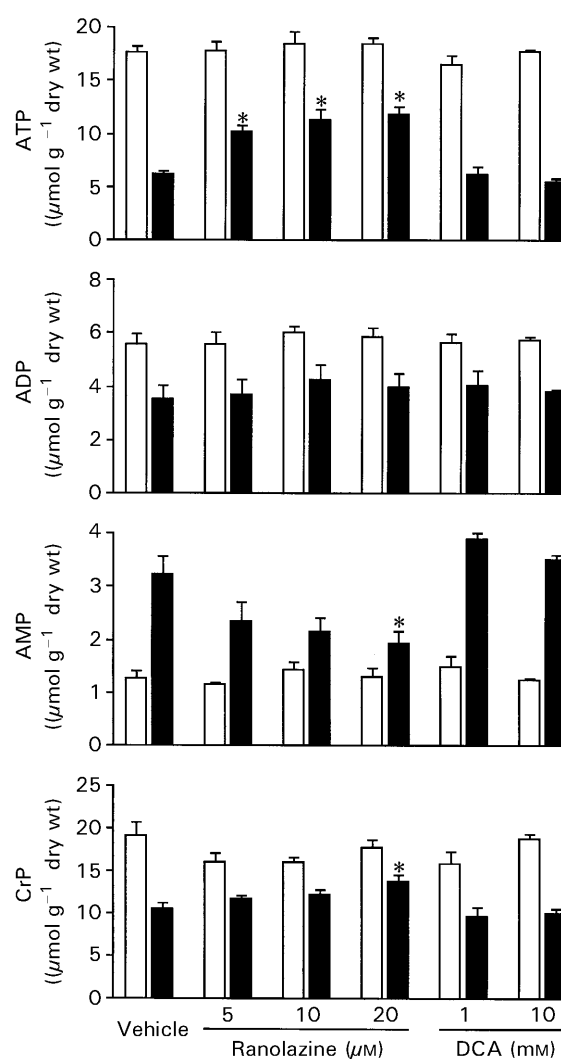
Figure 5. Effects of ranolazine and dichloroacetate (DCA) on palmitoyl-L-carnitine-induced changes in tissue levels of high-energy phosphates. The tissue levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and creatine phosphate (CrP) at the end of experiment (40 min after the start of vehicle, ranolazine or dichloroacetate infusion) were measured in normal, untreated (□) and palmitoyl-L-carnitine-treated (■) hearts. Each value is the mean ± s.e.m. results from 4 or 5 experiments in untreated groups and 7 or 8 experiments in palmitoyl-L-carnitine-treated groups. *$P < 0.05$ compared with vehicle.

Discussion

Ranolazine is a novel anti-ischaemic (or anti-anginal) agent with a piperazine structure. A characteristic pharmacological property of ranolazine is its cardio-protective action against ischaemic derangement without direct effect on haemodynamics such as cardiac function and blood pressure (Gralinski et al 1994; McCormack et al 1996; Matsumura et al 1998; Hara et al 1999). These findings suggest that the anti-ischaemic action of ranolazine is probably not because of improvement of myocardial oxygen balance, as a result of increased coronary flow or reduced cardiac mechanical function, or both. The primary mechanism of the anti-ischaemic action of ranolazine thus contrasts with that of nitrates, β-adrenoceptor antagonists, and Ca^{2+}-channel blockers. According to recent studies one mechanism of the cardiopro-tective action of ranolazine is acceleration of carbo-hydrate oxidation, resulting from activation of pyruvate dehydrogenase; the action of ranolazine on myocardial metabolism is to improve the efficiency of energy production and to attenuate the ischaemia-induced increase in lactate and H^+ in the myocardium (McCormack et al 1996; Hara et al 1999). The detailed mechanism of the anti-ischaemic action of ranolazine is, nevertheless, not fully understood.

Long-chain acylcarnitines, for example palmi-toyl-L-carnitine, are among the most important factors in the irreversible damage occurring in the ischaemic heart (Corr et al 1987, 1989; DaTorre et al 1991; Yamada et al 1994). Recent studies have revealed the occurrence of substances that protect the myocardium from damage induced by long-chain acylcarnitines (Hara et al 1996, 1997; Kang & Leaf 1996; Arakawa et al 1997; Xiao et al 1997). In this study we examined the effect of ranolazine on palmitoyl-L-carnitine-induced mechanical and metabolic derangement in the isolated perfused rat heart. The concentration of palmitoyl-L-carnitine used in the study ($4\,\mu$M) might damage the heart to the same extent as ischaemia—in terms of tissue accumulation of long-chain acylcarnitines (Busse-len et al 1988).

Palmitoyl-L-carnitine increased LVEDP, reduced LVDP (i.e. caused mechanical dysfunction), increased CPP (i.e. increased coronary resistance), reduced tissue levels of ATP and CrP, and increased tissue levels of AMP (i.e. caused meta-bolic derangement). These alterations induced by palmitoyl-L-carnitine were attenuated by ranolazine (5, 10, and $20\,\mu$M), suggesting that it has cardio-protective action against palmitoyl-L-carnitine-induced mechanical and metabolic derangement. The concentrations of ranolazine used in this study (5, 10, and $20\,\mu$M) also effectively reduced the myocardial derangement induced by ischaemia and reperfusion (Clarke et al 1993; Gralinski et al 1994; McCormack et al 1996).

In agreement with previous reports (Clarke et al 1993; Gralinski et al 1994; McCormack et al 1996), the concentration of ranolazine (5, 10, and $20\,\mu$M) used in the current study did not modify the mechanical function of the normal (palmitoyl-L-carnitine-untreated) heart. Ranolazine would not alter coronary flow under the conditions used in this study, because the hearts were perfused at a con-stant flow rate. It is unlikely, therefore, that the cardioprotective effect of ranolazine on palmitoyl-L-carnitine-induced myocardial derangement is a result of increased coronary flow or reduced energy consumption by the heart, or both. Ranolazine had no effect on tissue levels of high-energy phosphates in normal (palmitoyl-L-carnitine-untreated) heart, suggesting that the protective effect of ranolazine on palmitoyl-L-carnitine-induced derangement is not a result of preservation of energy induced by a favourable action on haemodynamics (i.e. an energy-sparing effect).

Ranolazine has been shown to stimulate carbo-hydrate oxidation by activation of pyruvate dehy-drogenase in the myocardium (Clarke et al 1993, 1996; McCormack et al 1996). According to Clarke et al (1996) ranolazine can activate pyruvate dehydrogenase in the isolated perfused rat heart only when fatty acid (such as palmitate) is present in the perfusion solution. Because we used a fatty acid-free perfusion solution (KHB buffer), activa-tion of pyruvate dehydrogenase would not occur, and therefore mechanisms other than action on carbohydrate metabolism contribute to the bene-ficial effect of ranolazine on palmitoyl-L-carnitine-induced derangement. To determine this possibi-lity, we examined whether dichloroacetate, which activates pyruvate dehydrogenase via inhibition of pyruvate dehydrogenase kinase (Stacpoole 1989; McVeigh & Lopaschuk 1990; Clarke et al 1996), would attenuate palmitoyl-L-carnitine-induced derangement. In contrast with ranolazine, dichlor-oacetate (1 mM) can activate pyruvate dehydro-genase in the myocardium, irrespective of the presence or absence of fatty acid in the perfusion solution (Clarke et al 1996). The results in the current study indicate that dichloroacetate, even at the higher concentration (10 mM), was less effec-tive than ranolazine at attenuating palmitoyl-L-carnitine-induced mechanical dysfunction and metabolic derangement. The action of ranolazine on carbohydrate metabolism might not, therefore, contribute to the cardioprotective effect of the drug against palmitoyl-L-carnitine-induced derange-ment, although we did not examine the effects of

ranolazine and dichloroacetate on pyruvate dehydrogenase activity in the palmitoyl-L-carnitine-treated heart. Further studies are needed to clarify the details of the mechanism of the protective action of ranolazine on palmitoyl-L-carnitine-induced derangement.

Palmitoyl-L-carnitine has been shown to induce endothelial dysfunction in the coronary artery, an effect considered to be responsible for myocardial derangement (Inoue et al 1994). Palmitoyl-L-carnitine caused a continuous and marked increase in CPP (i.e. increased coronary resistance) in the heart. Interestingly, in this study the palmitoyl-L-carnitine-induced increase in CPP was concentration-dependently attenuated by ranolazine, and so the cardioprotective action of ranolazine against the palmitoyl-L-carnitine-induced derangement might, at least in part, result from inhibition of palmitoyl-L-carnitine-induced endothelial dysfunction.

In conclusion, ranolazine attenuates mechanical dysfunction and metabolic derangement of the heart induced by palmitoyl-L-carnitine by mechanisms other than an energy-sparing effect or stimulation of carbohydrate oxidation.

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