Hemodynamic Basis for the Acute Cardiac Effects of Troglitazone in Isolated Perfused Rat Hearts

Masaki Shimoyama, Kazuhide Ogino, Yasushi Tanaka, Tadasu Ikeda, and Ichiro Hisatome

Troglitazone is a thiazolidinedione used for the treatment of NIDDM and potentially for other insulin-resistant disease states. Troglitazone has recently been shown to increase cardiac output and stroke volume in human subjects. These actions are thought to be mediated by the reduction of peripheral resistance, but a potential direct effect on cardiac function has not been studied. Therefore, we investigated the direct cardiac hemodynamic effects of troglitazone in isolated perfused rat hearts. Five groups of hearts were studied. Hearts were tested under isovolumetric contraction with a constant coronary flow, and troglitazone (0.2, 0.5, and 1.0 μmol) was administered by bolus injection. Peak isovolumetric left ventricular pressure (LVP_{max}), peak rate of rise of LVP (dP/dt_{max}), and peak rate of fall of LVP (dP/dt_{min}) were significantly increased 1 min after troglitazone administration in a dose-dependent manner, while the heart rate (HR) and coronary perfusion pressure (CPP) were significantly decreased ($P < 0.05$). HR was then fixed by pacing and/or CPP was fixed with nitroprusside to eliminate any effect of the two variables on the action of troglitazone. With constant HR and/or constant CPP, the effect of troglitazone on LVP_{max}, dP/dt_{max}, and dP/dt_{min} was still unchanged. In addition, the positive inotropic, positive lusitropic, and negative chronotropic actions of troglitazone were not influenced even when hearts were pretreated with prazosin, propranolol, or nifedipine. In conclusion, troglitazone has direct positive inotropic, positive lusitropic, negative chronotropic, and coronary artery dilating effects. The inotropic and chronotropic actions of troglitazone are not mediated via adrenergic receptors or calcium channels. These findings have important clinical implications for diabetic patients with congestive heart failure. ***Diabetes*** **48:609–615, 1999**

Diabetes is an independent risk factor for the development of coronary heart disease (1,2). Recently, hyperinsulinemia and insulin resistance have also been shown to be risk factors for coronary heart disease (3). To treat both diabetes and coronary heart disease, current practice is to reduce insulin resistance through diet and exercise and to augment insulin secretion with oral sulfonylureas. Although second-generation sulfonylureas may improve insulin sensitivity, their principal action is to increase pancreatic insulin secretion (4).

Troglitazone is a thiazolidinedione now available for the treatment of NIDDM and potentially other insulin-resistant disease states (5). Testing in diabetic animal models (6–9) and human clinical trials (10–12) has shown that troglitazone reduces hyperglycemia, HbA_{1c} levels, hyperinsulinemia, and high levels of free fatty acids and triglycerides. Recently, it was reported that troglitazone and other insulin-sensitizing thiazolidinedione drugs could decrease blood pressure in diabetic hypertensives (13) as well as in obese Zucker rats (9,14), fructose-fed rats (15,16), and high fat–fed or glucose-fed rats (17). One of the mechanisms involved is considered to be improvement of insulin resistance (13). However, pioglitazone (another thiazolidinedione) prevents hypertension without affecting insulin sensitivity in the one-kidney, one-clip Sprague-Dawley rat, a model of hypertension without insulin resistance (18,19). In addition, it has been suggested that a direct vascular effect may contribute to the blood pressure–lowering actions of pioglitazone in vivo, because its actions cannot be explained by alterations in whole-body insulin sensitivity (16). Quite recently, troglitazone was shown to have a direct effect on cardiac myocytes in vitro (20), and it also has a cardioprotective effect on basal and postischemic cardiac function in streptozotocin-induced diabetic rats (21). Furthermore, a statistically significant increase in stroke volume and cardiac output and a statistically significant decrease in diastolic blood pressure have been observed in troglitazone-treated patients, resulting from decreased peripheral resistance (22).

Thus, it is still unclear whether these hemodynamic effects of thiazolidinediones are mediated indirectly through changes in peripheral resistance or directly through some action on the heart. In the present study, we therefore investigated the direct cardiac hemodynamic effects of troglitazone in isolated perfused rat hearts and the mechanism of such hemodynamic effects.

RESEARCH DESIGN AND METHODS

Isolated heart preparation. Male Wistar rats (300–350 g, 12 weeks old) were used to make standard isolated isovolumetric heart preparations. All animals were handled in strict accordance with the Tottori University Guide for the Care and Use of Laboratory Animals. The procedure for creating isolated perfused rat hearts was similar to that described previously (23). Briefly, the rats were given heparin (1,000 U i.p.) and then heavily anesthetized with ketamine HCl (40 mg i.p.) and xylazine (2.0 mg i.p.). After bilateral sternotomy, the heart was rapidly excised from each animal and the aorta was cannulated for retrograde perfusion with a 14-gauge needle connected to a modified Langendorff perfusion system. This consisted of a warmed storage vat for perfusate, a Masterflex adjustable-speed rotary pump (model 7518-10), and a condenser. The vat and condenser were warmed by a constant temperature circulator (model T-80;

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CPP, coronary perfusion pressure; dP/dt_{max}, peak rate of rise of LVP; dP/dt_{min}, peak rate of fall of LVP; HR, heart rate; LVP, left ventricular pressure; LVP_{max}, peak isovolumetric LVP.

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Tokyo Rikakikai) set to heat the perfusate to 37°C. After rapid cannulation of the aorta, the coronary perfusion pressure (CPP) was held at 80 mmHg by maintaining a constant flow of modified Tyrode's solution (144 mmol/l sodium, 5 mmol/l potassium, 1.5 mmol/l calcium, 6 mmol/l HEPES, 0.9 mmol/l magnesium, 152 mmol/l chloride, and 5 mmol/l glucose). Lidocaine (5 µg/ml) was added to suppress ventricular ectopy. The pH was adjusted to 7.40, and the solution was equilibrated with 100% oxygen before use and bubbled continuously throughout the experiment. The perfusate was not recirculated. Ventricular function was assessed by measurement of the left ventricular pressure (LVP) with a fluid-filled latex balloon inserted into the ventricle through the mitral valve and held in place by a suture tied around the left atrium. The other end of the catheter was connected to a pressure transducer (model MP 5100; Baxter) for continuous measurement of LVP. A second transducer was connected to the perfusion line just before the heart and was used to measure CPP. Both transducers were connected to a Mac Lab model 200 to allow monitoring and recording of the heart rate (HR), LVP, and CPP. After attachment to the Langendorff perfusion system, the hearts were allowed to stabilize for at least 30 min, during which time LVP and CPP (constant at 80 mmHg) were monitored. The intraventricular balloon was inflated to give an end-diastolic pressure of 5 mmHg, and the balloon volume was held constant thereafter.

Drugs. Troglitazone was kindly supplied by Sankyo (Tokyo, Japan). Troglitazone was dissolved in 0.1 ml of medium (5% DMSO and 19% bovine serum albumin). Injection of 0.1 ml of the same medium without troglitazone was used as the control. Other drugs were purchased from Sigma (St. Louis, MO).

Experimental protocol. After the equilibration period, troglitazone was administered as a bolus injection directly into the condenser of the perfusion system (which contained 20 ml perfusate) to avoid changes in perfusion pressure, temperature, and pH due to the injection. Three doses of troglitazone were used: 0.2, 0.5, and 1.0 µmol, with the concentrations reaching the heart being 10, 25, and 50 µmol/l, respectively (n = 4 each). Injections were performed in random order.

The objective of these experiments was to assess the hemodynamic effects of troglitazone. Therefore, the hearts were divided into five groups, and the 5th group was further subdivided into four subgroups. Group 1 hearts received vehicle, 0.2, 0.5, and 1.0 µmol of troglitazone (n = 4 each, total n = 16) and the impact on HR, CPP, peak isovolumetric LVP (LVP_{max}), peak rate of rise of LVP (dP/dt_{max}), and peak rate of fall of LVP (dP/dt_{min}) was assessed after each injection. To eliminate the impact of variations of HR on contractility, relaxations, and coronary vascular resistance, hearts in group 2 (vehicle and 1.0 µmol troglitazone, n = 4 each, total n = 8) were paced at a constant rate of 240 beats/min before and after administration of troglitazone; this HR was greater than the maximal achieved in group 1. Next, to eliminate the effect of changes in coronary vascular resistance, the coronary bed was maximally dilated by adding sodium nitroprusside (5 µmol/l) to the perfusate in group 3 hearts (vehicle and 1.0 µmol troglitazone, n = 4 each, total n = 8). Next, to eliminate the effects of changes in both coronary vascular resistance and HR, group 4 hearts (vehicle and 1.0 µmol troglitazone, n = 4 each, total n = 8) were paced as in group 2, and the coronary bed was maximally dilated as in group 3. Finally, we assessed the effect of cross-reaction between troglitazone and other receptors on contractility, relaxation, and HR. After the coronary bed was maximally dilated as in group 3, prazosin (1 µmol/l), propranolol (1 µmol/l), or nifedipine (0.1 µmol/l) was added to the perfusate 30 min before administration of 1.0 µmol troglitazone and throughout the duration of the experiments; in addition, a 4th subgroup received no addition and vehicle instead of troglitazone (group 5, n = 4 each, total n = 20).

In every group, the impact of troglitazone on HR, LVP_{max}, dP/dt_{max}, and dP/dt_{min} was recorded at 1, 2, 3, 5, 10, 20, and 30 min after each injection. Changes of all parameters were expressed as percent changes from the baseline values before troglitazone infusion.

Statistical analysis. Comparisons of mean values were performed using analysis of variance, with individual differences assessed by Sheffe's multiple range test. Data are expressed as the mean ± SE, and statistical significance was defined as $P < 0.05$.

RESULTS

Table 1 summarizes the baseline values of CPP, HR, LVP_{max}, dP/dt_{max}, and dP/dt_{min} in the three groups of hearts. There were statistically significant differences among the groups for some of the parameters, but the magnitude of those differences was very small and would not be expected to cause any differences in the response to troglitazone.

Group 1 hearts. Troglitazone had an acute effect on LVP_{max}, dP/dt_{max}, dP/dt_{min}, HR, and CPP, as shown in Fig. 1. HR decreased significantly immediately after troglitazone injection and then gradually decreased further in a dose-dependent manner. CPP also decreased in a dose-dependent manner, and this effect continued for 30 min. At the highest dose (1.0 µmol), HR was decreased by an average of 8.2% immediately after injection and by an average of 10.2% at 30 min afterward ($P < 0.05$). CPP was decreased by an average of 44.1% at 30 min after injection ($P < 0.05$). On the other hand, LVP_{max} and dP/dt_{max} were increased significantly in a dose-dependent manner. At the highest dose, LVP_{max} was increased by 26.1%, with a corresponding increase of 38.8% in dP/dt_{max} ($P < 0.05$). In contrast to the effect on HR and CPP, these changes were rapid, reaching a maximum between 1 and 3 min after injection and returning to baseline within 10 min; the time course was similar for LVP_{max} and dP/dt_{max}. In addition, dP/dt_{min} was decreased significantly in a dose-dependent manner. At the highest dose, dP/dt_{min} was decreased by 62.6% ($P < 0.05$). We also confirmed the absence of significant hemodynamic effects of 0.1 µmol of troglitazone (data not shown). None of the parameters showed a significant change when the control vehicle was injected. These results indicated that troglitazone has a positive inotropic and lusitropic effect, a vasodilator effect, and a negative chronotropic effect. The mechanisms involved were not clear, however, as the independent effects of HR and coronary flow were not accounted for.

Constant HR protocol (group 2). The impact of troglitazone (1.0 µmol) on LVP_{max}, dP/dt_{max}, dP/dt_{min}, and CPP when HR was held constant (240 beats/min) is shown in Fig. 2. CPP and dP/dt_{min} decreased significantly, as was seen in group 1 ($P < 0.05$), while LVP_{max} and dP/dt_{max} increased significantly ($P < 0.05$). Thus, even when HR was fixed, myocardial contractility and relaxation were increased and coronary vascular resistance was decreased by troglitazone.

Constant CPP protocol (group 3). In group 3 hearts, the coronary bed was maximally dilated using nitroprusside (5 µmol/l) and CPP was kept at 80 mmHg, thus abolishing the vasodilatory effect of troglitazone. Figure 3 shows the inotropic, isovolumetric relaxant, and chronotropic effects of troglitazone. Troglitazone (1.0 µmol) had a significant effect on LVP_{max}, dP/dt_{max}, dP/dt_{min}, and HR, as was found in group 1 ($P < 0.05$). Therefore, even when coronary vascular resistance was fixed, the myocardial contractility state and relaxation were increased and HR was decreased by troglitazone.

Constant HR and constant CPP protocol (group 4). In group 4 hearts, the HR was fixed at 240 beats/min (as in group 2) and the coronary bed was maximally dilated with nitroprusside (as in group 3). However, troglitazone (1.0 µmol) still had a significant effect on LVP_{max}, dP/dt_{max}, and dP/dt_{min} (Fig. 4, $P < 0.05$). Thus, even when HR and coronary vascular resistance were controlled, troglitazone had direct inotropic and lusitropic actions.

Relationship between troglitazone and α-adrenergic receptors, β-adrenergic receptors, and calcium channels (group 5). In group 5 hearts, to assess the mechanism of the inotropic, lusitropic, and chronotropic actions of troglitazone, we added prazosin (1.0 µmol/l), propranolol (1.0 µmol/l), or nifedipine (0.1 µmol/l) to the perfusate and evaluated the influence of these agents on the hemodynamic effects of troglitazone. Because prazosin and nifedipine have a vasodilatory effect, which could complicate the hemodynamic actions of troglitazone, we used the group 3 protocol, holding CPP constant. Table 2 summarizes the baseline values of HR, LVP_{max}, dP/dt_{max}, and dP/dt_{min} in the hearts perfused

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TABLE 1
Baseline values of CPP, HR, LVP_{max}, dP/dt_{max}, and dP/dt_{min}

	Group 1	Group 2	Group 3	Group 4
n	16	8	8	8
CPP (mmHg)	81.3 ± 0.3	81.1 ± 0.6	Controlled	Controlled
HR (beats/min)	184.9 ± 2.7	Controlled	182.0 ± 3.9	Controlled
LVP_{max} (mmHg)	93.0 ± 3.6	84.0 ± 3.6	102.7 ± 1.1*	93.5 ± 4.3
dP/dt_{max} (mmHg/s)	2,637 ± 102	1,892 ± 160†	2,638 ± 44*	2,236 ± 112*†‡
dP/dt_{min} (mmHg/s)	–1,457 ± 72	–1,233 ± 60	–1,519 ± 42*	–1,266 ± 76‡

Data are means ± SE. *P < 0.05 vs. group 1; †P < 0.05 vs. group 2; ‡P < 0.05 vs. group 3.

with each receptor blocker. There were no statistically significant differences in these parameters, except in the nifedipine group. When nifedipine was added to the perfusate, HR changed from 194.8 ± 5.8 to 155.3 ± 2.9 beats/min, LVP_{max} changed from 116.7 ± 4.6 to 66.0 ± 5.5 mmHg, and dP/dt_{max} changed from 3,436 ± 254 to 1,605 ± 162 mmHg/s.

Figure 5 shows the inotropic, lusitropic, and chronotropic effects of troglitazone on hearts pretreated with prazosin (1.0 µmol/l), propranolol (1.0 µmol/l), or nifedipine (0.1 µmol/l). troglitazone (1.0 µmol) had a significant effect on LVP_{max}, dP/dt_{max}, dP/dt_{min}, and HR, as was also seen in group 3 (P < 0.05). These results indicated that the inotropic, lusitropic, and chronotropic actions of troglitazone were not mediated through α-adrenergic receptors, β-adrenergic receptors, or calcium channels.

DISCUSSION

The present study indicated that troglitazone has acute direct hemodynamic effects on isolated perfused rat hearts. Troglitazone had not only a vasodilatory effect, but also direct positive inotropic and lusitropic effects, as well as a negative chronotropic effect. To the best of our knowledge, this is the first report on the direct cardiac hemodynamic effects of troglitazone.

It has already been reported that insulin-sensitizing agents lower the blood pressure, suggesting that insulin resistance may contribute to the development of hypertension (9,11,14,24). While improvement of insulin resistance and decrease in plasma insulin level are proposed to be responsible for the reduction of blood pressure (13,25–27), it has also been reported that a direct effect may contribute to the hypotensive action of pioglitazone in vivo, because it could not be explained by an alteration of insulin sensitivity in some studies (16,19). In this study, coronary vasodilatation was observed in isolated hearts perfused without insulin, which meant that troglitazone had a direct vasodilatory effect independent of its influence on insulin sensitivity. Generally, troglitazone would be administered to diabetic or insulin-resistant patients. In this study, it remains unclear whether troglitazone exerts

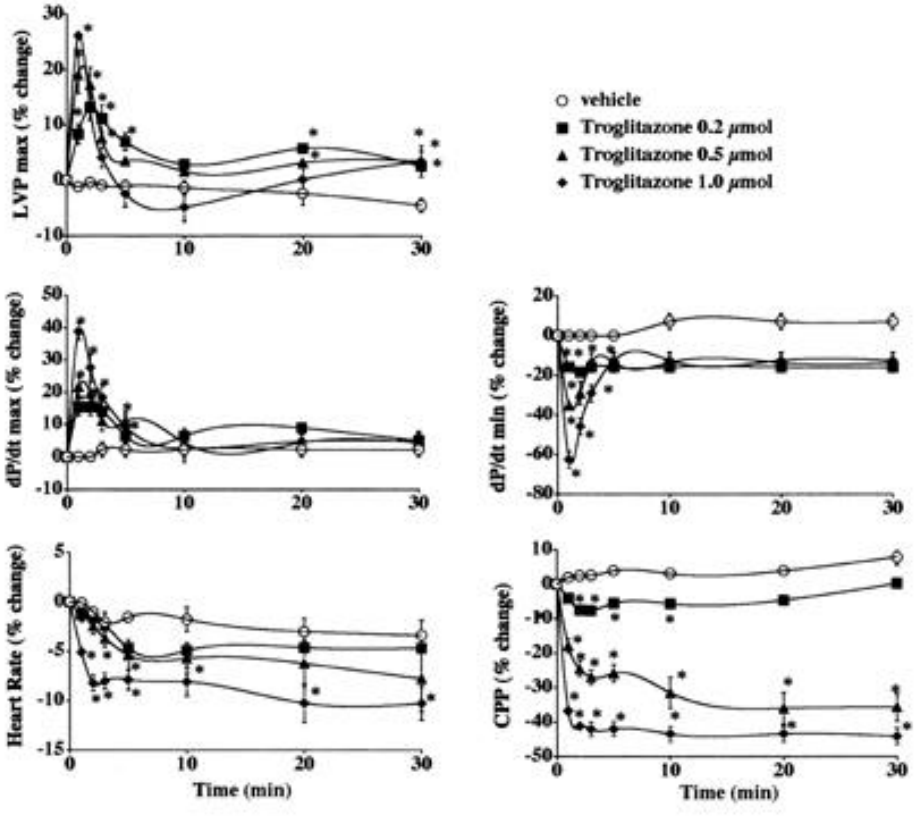

FIG. 1. The effects of troglitazone (0.2, 0.5, and 1.0 µmol, n = 4 each) on LVP_{max}, dP/dt_{max}, dP/dt_{min}, HR, and CPP with a constant coronary flow. LVP_{max} and dP/dt_{max} were increased in a dose-dependent manner after troglitazone administration. In contrast, HR, CPP, and dP/dt_{min} were decreased in a dose-dependent manner after troglitazone administration. There was no effect of infusion of 0.1 ml of vehicle. Results are expressed as percent changes from baseline values. *P < 0.05 vs. vehicle at each time.

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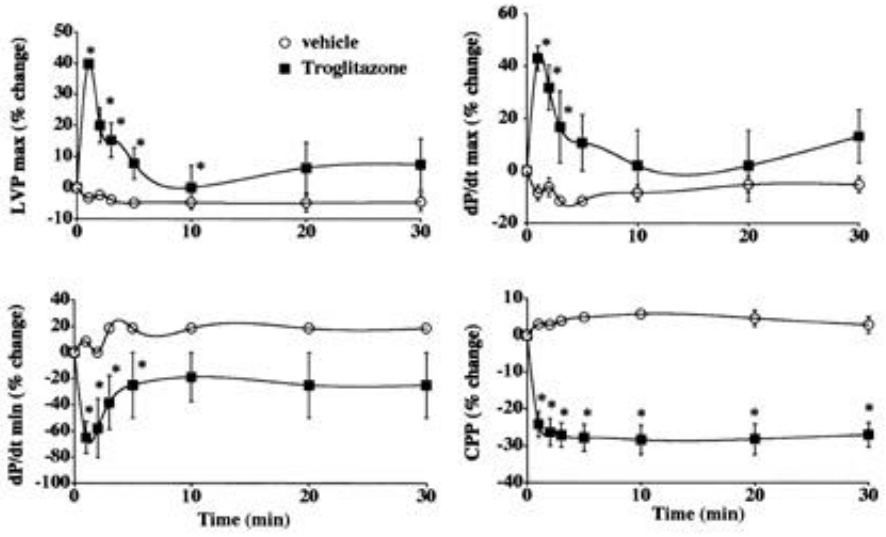

FIG. 2. The effects of troglitazone (1.0 µmol, n = 4 each) on LVP_{max}, dP/dt_{max}, dP/dt_{min}, and CPP with a constant HR (240 beats/min). LVP_{max} and dP/dt_{max} were significantly increased after troglitazone administration, while CPP and dP/dt_{min} were significantly decreased by troglitazone. There was no effect of infusion of 0.1 ml of vehicle. Results are expressed as percent changes from baseline values. *P < 0.05 vs. vehicle at each time.

cardiac hemodynamic effects in a diabetic state. Further studies will be necessary to clarify this issue.

Ren et al. (28), using fura-2–loaded myocytes, demonstrated that troglitazone can protect against high glucose–induced relaxation defects, perhaps through changes in intracellular Ca^{2+} handling. Other thiazolidinediones have also been shown to inhibit L-type calcium channels in vascular smooth muscle cells (16,19,29), an action that may contribute to the hypotensive effect of these drugs. In the present study, however, the hemodynamic effects of troglitazone (positive inotropic and negative chronotropic) were independent of calcium channels, because nifedipine, a calcium channel blocker, did not influence these actions of troglitazone. Although we did not evaluate the vasodilatory effect of troglitazone, because nifedipine also has a vasodilatory action, we confirmed that the calcium channel–blocking action of troglitazone was not involved in its direct cardiac effects (inotropic and chronotropic). A calcium channel–blocking action generally has a negative chronotropic effect, but troglitazone also had a positive inotropic effect, suggesting an independent mechanism unrelated to the calcium channels. It is possible that the concentration of nifedipine (0.1 µmol/l) used in this study was not high enough to block calcium channels completely, but this concentration decreased HR and contractility significantly and was the maximum concentration that did not induce cardiac toxicity. Baseline values of LVP_{max}, dP/dt_{max}, dP/dt_{min}, and HR were all affected by the high dose of nifedipine, which might interfere with the hemodynamic effects of troglitazone. We confirmed the same hemodynamic effects of troglitazone in the presence of a low concentration of nifedipine (0.01 µmol/l), which did not significantly affect baseline hemodynamic parameters (data not shown). However, whether or not blockade of calcium entry is involved in the vasodilatory effects of troglitazone remains to be determined.

Ghazzi et al. (22) reported that troglitazone enhanced cardiac output and stroke volume in patients with NIDDM, but this may possibly have been a result of decreased arterial pressure and peripheral resistance. In the present study, troglitazone increased LVP_{max} and dP/dt_{max} immediately but transiently. It is well known that both HR and CPP exert an independent influ-

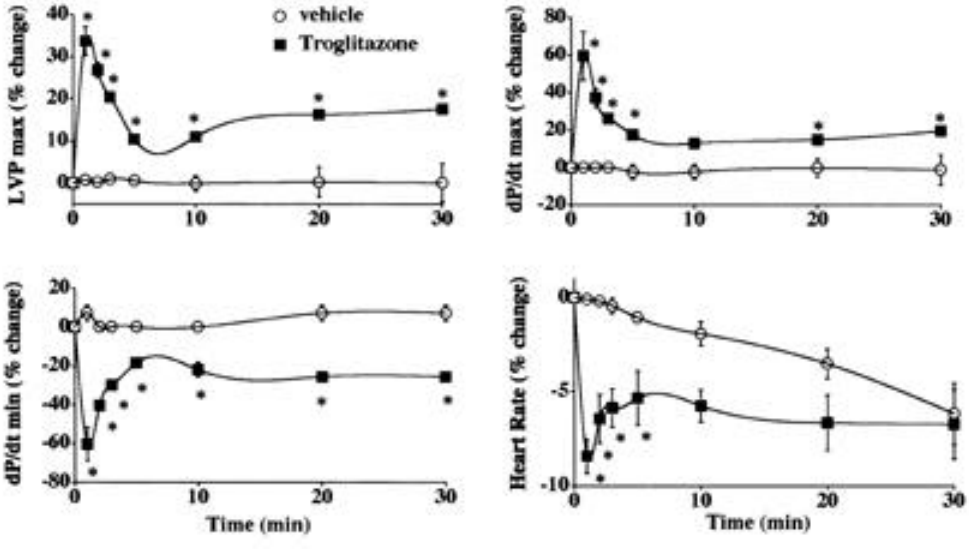

FIG. 3. The effects of troglitazone (1.0 µmol, n = 4 each) on LVP_{max}, dP/dt_{max}, dP/dt_{min}, and HR after the coronary bed was dilated with nitroprusside. LVP_{max} and dP/dt_{max} were significantly increased by troglitazone, while HR and dP/dt_{min} were significantly decreased. There was no effect of infusion of 0.1 ml of vehicle. Results are expressed as percent changes from baseline values. *P < 0.05 vs. vehicle at each time.

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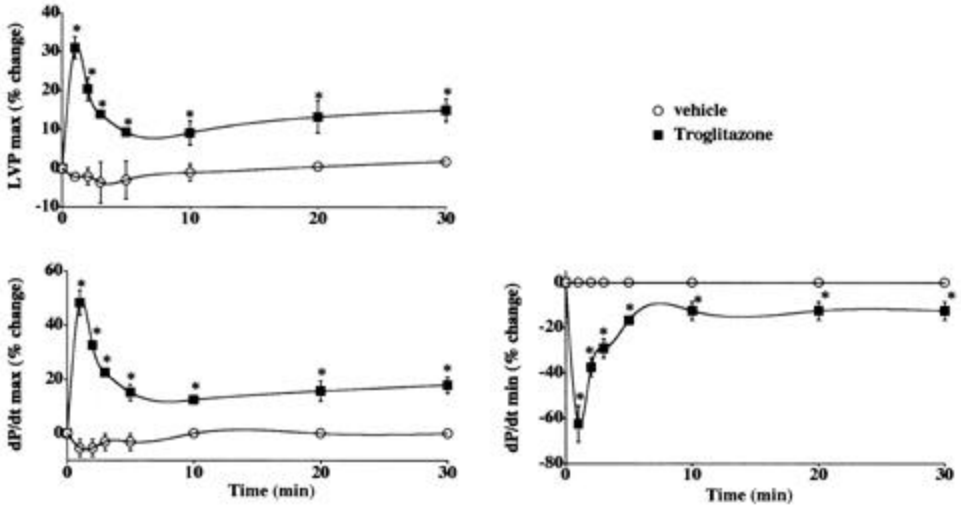

FIG. 4. The effects of troglitazone (1.0 µmol, n = 4 each) on LVP_{max}, dP/dt_{max}, and dP/dt_{min} in hearts with a constant HR (240 beats/min) and constant CPP after coronary bed dilation with nitroprusside. LVP_{max} and dP/dt_{max} were significantly increased and dP/dt_{min} was significantly decreased by troglitazone. There was no effect of infusion of 0.1 ml of vehicle. Results are expressed as percent changes from baseline values. *P < 0.05 vs. vehicle

ence on the contractile state of the ventricle, and coronary hypoperfusion can itself lead to myocardial dysfunction. In the present study, we confirmed the independent inotropic effect of troglitazone on isolated perfused hearts with a constant CPP and constant HR. Furthermore, troglitazone increased contractility despite a decrease of CPP, so it had a direct positive inotropic effect.

Several classes of compounds are known to act as vasodilators and inotropes. cAMP has a positive inotropic effect and a vasodilatory effect, which are similar to those of troglitazone. However, the β-adrenergic receptor blocker propranolol, which is well known to inhibit an increase of cAMP, did not inhibit this inotropic effect. There is a possibility that troglitazone increased cAMP through other signals. However, an increase of cAMP generally leads to an increase in HR, whereas troglitazone decreased HR in this study. Thus, the direct positive inotropic effect of troglitazone may not be mediated via the β-adrenergic receptor in isolated perfused hearts. The diabetic state involves excess oxidative stress (30), which is thought to alter contractile pump activity in the heart (31,32). Troglitazone has a scavenging effect on reactive oxygen species that tend to be radicals (33), and this may be one mechanism of its inotropic effect. Recently, it was reported that the vasorelaxant effect of troglitazone was abolished in the presence of indomethacin, which indicates a prostaglandin pathway (34). This might be a mechanism involved in the vasodilating effects of troglitazone. No available data, however—including our results—have been published concerning the cardiac effects.

In the present study, troglitazone reduced HR, a finding that is consistent with a previous report (35). On the other hand, Ogihara et al. (13) did not observe any effect of this drug on the pulse rate. These results and our data imply that at least troglitazone does not have a positive chronotropic effect. Because calcium channel blockers generally decrease HR, this negative chronotropic effect might have been explained by a calcium channel–blocking effect of troglitazone. However, we confirmed that nifedipine did not inhibit the negative chronotropic effect of troglitazone. Thus, this effect is not mediated through calcium channels, although the actual calcium channel–blocking effect of troglitazone may remain unclear, as mentioned above.

Thus, troglitazone has unique hemodynamic effects, including positive inotropic, negative chronotropic, and vasodilatory effects. There might be two or more mechanisms to explain the complicated effects of troglitazone noted in this study. There was a chronological discrepancy between the appearance of the inotropic effect and of the vasodilatory and chronotropic effects. While LVP_{max} and dP/dt_{max} increased immediately after troglitazone administration and returned to baseline within 10 min, CPP and HR decreased and did not return to baseline until 30 min after troglitazone administration. These differences in time course might support the existence of multiple mechanisms.

The acute changes in cardiac function observed in this study may not be identical to those occurring after longer-term treatment with troglitazone. In previous studies, blood pressure was decreased via vasodilating effects and insulin sensitivity was increased after long-term treatment with troglitazone (13,35).

TABLE 2
Baseline values of HR, LVP_{max}, dP/dt_{max}, and dP/dt_{min} in hearts pretreated with various blockers

	Vehicle	TRO	TRO + prazosin	TRO + propranolol	TRO + nifedipine
n	4	4	4	4	4
HR (beats/min)	184.5 ± 4.7	179.5 ± 6.7	166.9 ± 4.9	160.4 ± 3.4*	155.3 ± 2.9*
LVP_{max} (mmHg)	102.6 ± 0.9	102.8 ± 2.3	105.2 ± 2.6	113.9 ± 4.5	66.0 ± 5.5*
dP/dt_{max} (mmHg/s)	2,638 ± 66	2,637 ± 67	2,695 ± 144	2,639 ± 57	1,605 ± 162*
dP/dt_{min} (mmHg/s)	–1,491 ± 66	–1,548 ± 58	–1,433 ± 110	–1,663 ± 57	–860 ± 57*

Data are means ± SE. *P < 0.05 vs. vehicle. TRO, troglitazone.

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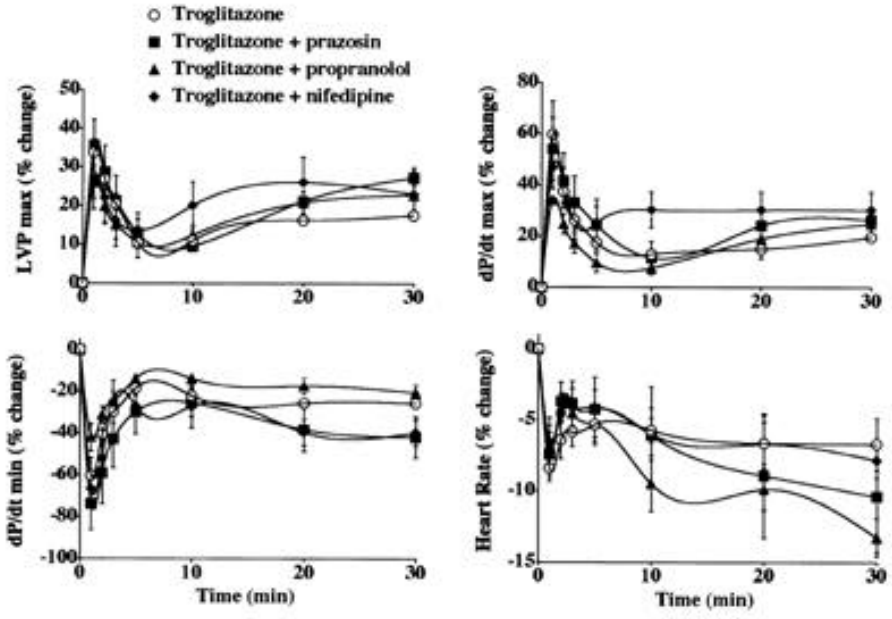

FIG. 5. The effects of troglitazone (1.0 µmol, n = 4 each) on LVP_{max}, dP/dt_{max}, dP/dt_{min}, and HR in hearts with the coronary bed dilated by nitroprusside. Prazosin (1.0 µmol/l), propranolol (1.0 µmol/l), or nifedipine (0.1 µmol/l) was added to the perfusate. troglitazone (1.0 µmol) had a significant effect on LVP_{max}, HR, dP/dt_{max}, and dP/dt_{min}, as seen in Fig. 3, and those parameters were not statistically affected by prazosin, propranolol, or nifedipine. Results are expressed as percent changes from baseline values.

As demonstrated in this study, the inotropic effect of troglitazone was transient, but the vasodilating effect of troglitazone persisted for 30 min. This might imply that the main hemodynamic effect of longer-term treatment with troglitazone is vasodilation, but not inotropy.

In conclusion, we demonstrated that troglitazone had direct positive inotropic and lusitropic actions, a negative chronotropic action, and a vasodilatory action on isolated perfused rat hearts. These actions were not mediated through α-adrenergic receptors, β-adrenergic receptors, or calcium channels. This is a novel cardioprotective action, in which the positive inotropic and vasodilatory effects occur without increasing HR. Such hemodynamic effects may be beneficial for NIDDM patients with heart failure. However, further investigations are needed to clarify the hemodynamic effect of troglitazone in the diabetic state and the mechanisms involved.

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