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Effects of MCI-154, a calcium sensitizer, on cardiac function in endotoxemic rabbits[1]

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KEY WORDS heart; endotoxins; left ventricular function; endotoxemia; cardiotonic agents; calcium; MCI-154

ABSTRACT

AIM: To observe the effects of MCI-154, a calcium sensitizer, on cardiac function after endotoxic shock. **METHODS**: The rabbits were intravenously injected with MCI-154 0.1 $mg \cdot kg^{-1}$ at 10 h after the administration of endotoxin 1.0 $mg \cdot kg^{-1}$, followed by a continuous infusion of normal saline (NS) 50 $mL \cdot kg^{-1}$ + MCI-154 0.1 $mg \cdot kg^{-1}$. During this process, the parameters of cardiac function were measured. **RESULTS**: Ten hours after the endotoxin injection, heart rate (HR) increased noticeably while the mean arterial blood pressure (MAP), left ventricular systolic pressure (LVSP), isovolumetric pressure (IP), myocardial contractility (MC), and the area of p-dp/dt_{max} vector loop (Lo) were all markedly decreased. Treatment with NS 50 $mL \cdot kg^{-1}$ alone had slight effects on these parameters. LVSP, IP, MC, and Lo were all markedly increased while HR did not obviously change and left ventricular end-diastolic pressure (LVEDP) was reduced markedly following MCI-154 administration in endotoxic shock rabbits. The parameters of MC were improved nearly to the same values as in sham shock group and were markedly higher than in NS treated group. **CONCLUSION**: MCI-154 exerts remarkable therapeutic effects on cardiac dysfunction after endotoxic shock.

INTRODUCTION

It has been shown that Ca^{2+} overload in myocytes and the decrease of Ca^{2+} sensitivity in myofilament are important etiological factors for cardiac dysfunction during sepsis/septic shock[1,2]. To improve the cardiac dysfunction under this condition, it seems more desirable to restore Ca^{2+} sensitivity of myofilaments by means of a calcium sensitizer than to increase the intracellular free Ca^{2+} concentration by maneuvers that are likely to cause Ca^{2+} overload. The positive inotropic agents currently used in the clinic setting exert their effects mainly by ways of increasing Ca^{2+} concentration in myocytes, but not through increasing the Ca^{2+} sensitivity of cardiac contractile system. Therefore, these agents are not so desirable in the treatment of cardiac dysfunction during sepsis/septic shock. As a newly developed cardiotonic agent, MCI-154 was reported to have strong inotropic and little chronotropic effects along with a peripheral vasodilative property[3,4]. It was showed that MCI-154 produced its cardiotonic effects without the involvement of α or β adrenergic, histaminergic, muscarinic receptors or Na^+, K^+-pump[5,6]. A phosphodiesterase (PDE)-inhibition mechanism was also excluded, because MCI-154 did not obviously affect the PDE activity and myocardial tissue cyclic AMP (cAMP) content in canine ventricular muscle[7]. Experimental evidences indicated that MCI-154 exerted its positive inotropic action mainly by a direct enhancement of troponin C (TnC) Ca^{2+} binding and/or a direct activation of actin-myosin reaction[8,9,10,11]. The enhancement of Ca^{2+} binding to TnC results in an increase in myocardial contractility. Therefore, MCI-154 may be a beneficial agent for increasing the cardiac contractile force without the danger of exacerberating Ca^{2+} overload in the myocardial cells.

As yet, however, most experimental studies of MCI-154 were focused on normal heart and congestive failure heart. It has not been proven whether MCI-154 improves cardiac dysfunction under the condition of sepsis/septic shock. According to the pharmacological

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characteristics, it seems to be an ideal cardiotonic agent for the treatment of cardiac dysfunction during sepsis/septic shock. To verify this speculation, we observed the effects of MCI-154 on the cardiac function in endotoxic shock rabbits.

MATERIALS AND METHODS

Twenty-four Japanese rabbits of either sex, weighing 2.5 – 3.0 kg, were used in this experiment. The animals were supplied by Department of Experimental Animals, Research Institute of Surgery (Grade Ⅱ, Certificate № 25301070). The rabbits were fasted for 12 h prior to the experiment but were allowed water *ad lib*. Before the experiment, the rabbits were randomly divided into three groups of nine animals each: group Ⅰ, sham shock rabbits treated with normal saline (NS) 50 mL·kg^{-1}; group Ⅱ, endotoxic shock rabbits treated with NS 50 mL·kg^{-1} alone; group Ⅲ, endotoxic shock rabbits treated with intravenous injection of MCI-154 0.1 mg·kg^{-1}, followed by a continuous infusion of NS 50 mL·kg^{-1} + MCI-154 0.1 mg·kg^{-1}. Endotoxic shock or sham shock was induced by a slow injection of endotoxin 1.0 mg·kg^{-1} (*E Coli*, O111: B4, Sigma) or an equal volume of NS respectively via a marginal ear vein. Nine hours after the injection of endotoxin or NS, the rabbits were anesthetized with sodium pentobarbital (30 mg·kg^{-1}, iv), the left femoral artery was cannulated with a polyethylene catheter which was attached to a blood pressure transducer for the purpose of monitoring the mean arterial pressure (MAP) in a four-channel recorder (RM-6200, Nihon Khoden, Japan). The left femoral vein was cannulated and connected to a peristaltic pump (LKB-7662, Sweden) for giving medicine and infusion of solution at a rate of 0.7 mL·min^{-1}. The left ventricle was catheterized through the right carotid artery for observing hemodynamics. All the catheters were filled with heparinized saline (25 kU·L^{-1}). At the end of operation, the rabbits were heparinized (500 U·kg^{-1}). The animals were stabilized for 20 – 30 min. Ten hours after the injection of endotoxin or NS (time 0), treatment was given according to the protocols. Parameters were recorded at time 0, and at different time points following treatment via a hemodynamic analyzer (computer controlled hemodynamic analysis system). These parameters included heart rate (HR), MAP, left ventricular systolic pressure (LVSP), isovolumetric pressure (IP), left ventricular end-diastolic pressure (LVEDP), maximal rate of left ventricular systolic pressure changes ($LV \pm dp/dt_{max}$), the velocity of cardiac contractile element shortening at 5.33 kPa (40 mmHg) of left intraventricular pressure (V_{ce40}), the physiological maximal velocity (Vpm), and the area of p-dp/dt vector loop (Lo)[12].

MCI-154, 6-[4-(4′-pyridyl) aminophenyl]-4, 5-dihydro-3 (2H)-pyridazinone hydrochloride (supplied by College of Pharmacy, Second Military Medical University, Shanghai, China), was a grey powder, M_r 266, mp 250 – 251 ℃, Purity > 99.5 %. All other drugs were of analytical grade and were purchased from Chongqing Medicine Company. This study was performed in accordance to the Chongqing Council for Animal Research Guidelines for the Use of Experimental Animals.

The data are presented as $\bar{x} \pm s$. Statistical differences between groups were assessed by ANOVA. $P < 0.05$ was considered statistically significant.

RESULTS

General conditions and changes in HR There were no significant differences among the three groups with regard to body weight. After injection of endotoxin, endotoxic shock symptoms appeared in rabbits. They moved less, became tachypneic and progressively lethargic. Some animals had diarrhea, or even bloody diarrhea. During the experimental period, all the animals in group Ⅰ roup Ⅲ survived. One animal died 4 h after treatment in group Ⅱ. HR increased markedly following endotoxin injection. During the whole observation, HR in group Ⅱ and group Ⅲ was higher than that of group Ⅰ (< 0.01), but there was no statistical difference between group Ⅱ and group Ⅲ ($P > 0.05$) (Tab 1).

Changes in blood pressure The changes in MAP, LVSP, IP, and LVEDP in three groups were shown in Tab 1. Ten hours after endotoxin injection, MAP, LVSP, and IP decreased markedly, and LVEDP increased obviously as compared with the values of group Ⅰ ($P < 0.01$). Although MAP, LVSP, and IP increased following NS alone treatment, the increase was small, whereas LVEDP kept increasing continuously. However, after the treatment with MCI-154, the values of LVSP and IP were higher than in group Ⅱ throughout the observation period ($P < 0.05$). At 2 h after MCI-154 treatment, MAP in group Ⅲ became obviously higher than that of group Ⅱ ($P < 0.05$). LVEDP was lower than that of group Ⅱ at each time point during the whole observation following MCI-154 treatment ($P < 0.05$) (Tab 1).

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Tab 1. Effects of MCI-154 on HR, MAP, LVSP, IP, and LVEDP in endotoxemic rabbits. HR: heart rate; MAP: mean arterial blood pressure; LVSP: left ventricular systolic pressure; IP: isovolumetric pressure; LVEDP: left ventricular end-diastolic pressure. Ⅰ: sham shock group; Ⅱ: endotoxic shock group treated with NS alone; Ⅲ: endotoxic shock group treated with MCI-154 + NS. 0: time 0, 10 h after injection of endotoxin or equal volume of NS. $^bP<0.05$, $^cP<0.01$ *vs* Ⅰ, $^eP<0.05$ *vs* Ⅱ.

	Group	Time after treatment/h					
		0	0.5	1	2	4	6
	Ⅰ	327 ± 28	338 ± 21	335 ± 27	327 ± 24	316 ± 28	315 ± 25
HR,	Ⅱ	396 ± 37^c	396 ± 30^c	384 ± 25^c	371 ± 27^c	382 ± 31^c	401 ± 35^c
beat/min	Ⅲ	402 ± 34^c	398 ± 28^c	394 ± 26^c	387 ± 23^c	388 ± 29^c	387 ± 31^c
	Ⅰ	13.1 ± 0.9	14.1 ± 0.9	15.0 ± 1.2	14.9 ± 1.0	14.6 ± 0.9	14.2 ± 0.9
MAP,	Ⅱ	8.2 ± 1.2^c	9.4 ± 1.2^c	9.9 ± 1.2^c	9.8 ± 0.8^c	9.1 ± 0.8^c	8.0 ± 1.1^c
kPa	Ⅲ	8.4 ± 1.1^c	8.9 ± 1.1^c	9.2 ± 1.0^c	11.3 ± 0.9^{be}	11.0 ± 0.8^{be}	10.9 ± 0.9^{be}
	Ⅰ	16.6 ± 2.0	20.2 ± 2.3	20.4 ± 2.5	19.7 ± 2.3	18.9 ± 1.8	18.7 ± 2.1
LVSP,	Ⅱ	12.1 ± 1.1^c	13.8 ± 1.4^c	14.2 ± 1.5^c	14.6 ± 1.6^c	13.1 ± 2.0^c	11.8 ± 1.6^c
kPa	Ⅲ	11.9 ± 1.0^c	17.7 ± 2.0^{be}	17.5 ± 1.7^{be}	17.1 ± 1.5^{be}	15.3 ± 1.4^{be}	14.2 ± 1.2^{be}
	Ⅰ	15.2 ± 1.3	17.2 ± 1.2	17.3 ± 1.2	16.9 ± 1.0	16.6 ± 1.0	15.5 ± 1.1
IP,	Ⅱ	9.4 ± 1.6^c	11.4 ± 1.9^c	11.9 ± 2.1^c	11.2 ± 1.6^c	10.2 ± 1.4^c	9.7 ± 1.3^c
kPa	Ⅲ	9.2 ± 1.5^c	13.7 ± 1.2^{be}	14.2 ± 1.5^{be}	13.7 ± 1.4^{be}	12.9 ± 1.3^{be}	12.1 ± 1.2^{be}
	Ⅰ	0.20 ± 0.09	0.25 ± 0.07	0.28 ± 0.08	0.27 ± 0.08	0.29 ± 0.06	0.29 ± 0.08
LVEDP,	Ⅱ	0.92 ± 0.17^c	1.08 ± 0.25^c	1.20 ± 0.32^c	1.33 ± 0.38^c	1.45 ± 0.36^c	1.57 ± 0.32^c
kPa	Ⅲ	0.91 ± 0.19^c	0.65 ± 0.15^{be}	0.67 ± 0.12^{be}	0.75 ± 0.14^{be}	0.86 ± 0.26^{be}	0.95 ± 0.21^{be}

Changes in left ventricular myocardial contractility After endotoxic shock, left ventricular myocardial contractility decreased as was reflected by decreases of LV ± dp/dt_{max}, V_{pm}, and V_{ce40}. Treatment with NS alone had slight effects on the above parameters. At 0.5 h and 1 h after NS alone treatment, LV + dp/dt_{max}, LV − dp/dt_{max}, V_{pm} and V_{ce40} were increased by about: 24 % and 18 %, 19 % and 13 %, 15 % and 10 %, 24 % and 18 %, respectively. Moreover, at 2 h, the values of the above parameters recovered nearly to the value at time 0. However, these parameters increased markedly in MCI-154 treated group. At 0.5 h and 1 h, they were restored nearly to the levels of group Ⅰ and were significantly higher than those of group Ⅱ ($P<0.05$, $P<0.01$, respectively), the percent increases in the parameters compared with those at time 0 were respectively as follows: LV + dp/dt_{max}, 52 % and 49 %; LV-dp/dt_{max}, 67 % and 48 %; V_{pm}, 92 % and 79 %; V_{ce40}, 82 % and 74 %. Furthermore, they were all higher than those in group Ⅱ during the remainder of the observation period ($P<0.05$, $P<0.01$, respectively) (Tab 2).

Changes in Lo After endotoxic shock, Lo was markedly decreased. Following NS alone treatment, the increase in Lo was not marked. However, in MCI-154 + NS treated group, the increase of Lo was remarkable. At 0.5 h and 1 h, the values in Lo in group Ⅲ increased nearly to the level of group Ⅰ. Moreover, the value of Lo at each time point after MCI-154 + NS treatment was higher than that of NS alone treated group ($P<0.05$, $P<0.01$, respectively) (Tab 2).

DISCUSSION

It has been shown that myocardial dysfunction occurred during sepsis/septic shock, at an early stage. Hung and Lew[2] have reported that endotoxic shock led to intrinsic myocardial depression independent of alterations in loading conditions or extrinsic factors, suggesting that the myocardial dysfunction was primary. The precise mechanisms of the myocardial dysfunction during endotoxic shock are not clear. Studies have indicated that myocytes from endotoxin-treated rabbits had depressed shortening, peak rate of shortening, and peak rate of lengthening over a wide [Ca^{2+}] range[2]. In an isolated perfused heart model of septic rats, Dong *et al*[1] demonstrated that Ca^{2+} contents in myocardium and mitochondria increased by 190 % and 332 %, respectively. These studies suggested that decreased myofilament sensitivity to Ca^{2+} and Ca^{2+} overload in myocytes was involved in the pathogenesis of myocardial dysfunction during sepsis/septic shock.

Tab 2. Effects of MCI-154 on LV ± dp/dt_{max}, V_{pm}, V_{ce40}, and Lo in endotoxemic rabbits. LV ± dp/dt_{max}: maximal rate of left ventricular systolic pressure changes; V_{pm}: the physiological maximal velocity; V_{ce40}: the velocity of cardiac contractile element shortening at 5.33 kPa (40 mmHg) of left intraventricular pressure; Lo: the area of p-dp/dt vector loop. $^bP<0.05$, $^cP<0.01$ *vs* Ⅰ; $^eP<0.05$, $^fP<0.01$ *vs* Ⅱ.

	Group	Time after treatment/h					
		0	0.5	1	2	4	6
+ dp/dt_{max}, kPa/s	Ⅰ	978 ± 140	1001 ± 106	959 ± 114	941 ± 132	939 ± 126	978 ± 140
	Ⅱ	653 ± 84^c	810 ± 118^b	772 ± 126^b	729 ± 129^c	636 ± 119^c	564 ± 107^c
	Ⅲ	630 ± 88^c	960 ± 138^e	939 ± 140^e	862 ± 105^f	742 ± 107^{be}	678 ± 111^{be}
-dp/dt_{max}, kPa/s	Ⅰ	803 ± 94	838 ± 98	821 ± 96	815 ± 89	790 ± 89	755 ± 79
	Ⅱ	458 ± 81^c	546 ± 105^c	518 ± 92^c	487 ± 87^c	440 ± 85^c	396 ± 73^c
	Ⅲ	476 ± 104^c	795 ± 106^f	704 ± 115^f	612 ± 102^{be}	575 ± 84^{be}	509 ± 86^{be}
V_{pm}, l/s	Ⅰ	10.5 ± 1.6	11.1 ± 1.7	10.9 ± 1.4	10.6 ± 1.2	10.0 ± 1.3	9.5 ± 1.2
	Ⅱ	6.1 ± 1.3^c	7.0 ± 1.0^c	6.7 ± 1.0^c	6.4 ± 1.1^c	5.5 ± 1.1^c	4.7 ± 1.0^c
	Ⅲ	5.3 ± 1.7^c	10.2 ± 1.3^f	9.5 ± 1.2^f	8.5 ± 1.0^{be}	7.2 ± 0.8^{be}	6.5 ± 1.3^{be}
V_{ce40}, l/s	Ⅰ	7.8 ± 1.3	8.2 ± 1.3	8.2 ± 1.3	7.9 ± 1.3	7.5 ± 1.0	7.1 ± 0.9
	Ⅱ	3.3 ± 0.8^c	4.1 ± 1.0^c	3.9 ± 0.6^c	3.6 ± 0.9^c	3.5 ± 0.9^c	3.1 ± 0.7^c
	Ⅲ	3.4 ± 0.9^c	6.2 ± 1.4^{be}	5.9 ± 1.1^{be}	5.6 ± 1.1^{be}	5.3 ± 0.8^{be}	4.7 ± 1.1^{be}
Lo	Ⅰ	98 ± 19	101 ± 13	108 ± 13	105 ± 14	102 ± 14	96 ± 16
	Ⅱ	54 ± 10^c	63 ± 9^c	62 ± 8^c	58 ± 10^c	54 ± 9^c	48 ± 10^c
	Ⅲ	56 ± 9^c	95 ± 13^f	96 ± 15^f	90 ± 11^f	82 ± 10^{be}	65 ± 10^{be}

Improvement of cardiovascular function is always a fundamental treatment in shock so the use of positive inotropic agents is sometimes unavoidable. Although there are established regimens for the treatment of myocardial dysfunction using cardiotonic agents now available in clinic setting, they may not be the best therapy for cardiac depression caused by sepsis/septic shock in view of Ca^{2+} overload and the decrease in Ca^{2+} sensitivity in myocardial contractile system. An ideal positive inotropic agent should be capable of increasing the myocardial contractility effectively without further elevation of Ca^{2+} concentration in myocytes. However, all the positive inotropic agents in current use, including the cardiac glycosides, catecholamines and phosphodiesterase inhibitors, act through a mechanism of increasing intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). It would be of clinic significance to survey novel cardiotonic agents that can be effectively and safely used in the treatment of cardiac dysfunction during sepsis/septic shock.

In this study, we observed the effects of MCI-154 on cardiac dysfunction in endotoxic shock of rabbits. The results showed that there was a cardiac depression during endotoxic shock with decreased MAP, LVSP, and IP, a higher LVEDP and lower LV ± dp/dt_{max}, V_{pm}, V_{ce40}, and Lo. Although MAP, LVSP, IP, and the parameters of myocardial contractility were increased following NS treatment, the increase was small and transient, and LVEDP kept increasing. These results indicated that the cardiac depression during endotoxic shock was not caused mainly by a decrease in venous return and reduced preload. However, following the administration of MCI-154, LVSP, IP, LV ± dp/dt_{max}, V_{pm}, V_{ce40}, and Lo all increased noticeably with an obvious decrease in LVEDP. Soon after MCI-154 treatment, all the parameters of cardiac contractility was increased nearly to the levels of sham shock group, higher than the values of NS alone treated group. During the whole observation, the beneficial effects of MCI-154 + NS on cardiovascular function were much more than those of NS alone. HR was not higher following MCI-154 administration as compared with NS alone treated group. The results suggested that MCI-154 could remarkably improve the cardiac systolic and diastolic function with slight effects on HR in endotoxic shock. Our results are similar to the experiment conducted by Teramura *et al*[13]. They showed that left ventricular contractility was improved by MCI-154 to an extent similar to that in the control state, and that MCI-154 also accelerated left ventricular relaxation in a pacing-induced heart failure model of dog. The mechanisms for the improvement of left ventricular systolic function after MCI-154 treatment in our study are not clear but may involve the increased Ca^{2+} sensitivity of myofilament leading to increased contractility of myocardium. The improvement in diastolic

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function (increased-dp/dt_{max}, decreased LVEDP) may be caused by an increase in the elastic recoil capacity of myocardial muscles through augmenting left ventricular function[14]. Additionally, the pharmacological action of MCI-154 to dilate the peripheral blood vessels and reduce the peripheral vascular resistance may also contribute to the improvement.

The relatively smaller increases in MAP may be explained by the fact that MCI-154 also functioned as a vasodilator. It is well-known that one cause contributing to the hypotension in sepsis/septic shock is the pathophysiological consequence of vasodilation and reduced venous return to the heart. Elevation of systemic blood pressure has always been an important step for antishock treatment. Fluid infusion is the basic therapeutic strategy, especially when cardiac depression exists. Under the circumstances, the addition of cardiotonic agents is also necessitated[15]. It is possible that the vasodilatory action of MCI-154 may have a negative effect on systemic blood pressure when used in sepsis/septic shock. Can such a therapeutic defect of MCI-154 be overcome by adequate fluid infusion? Our results showed that the values of MAP at 2 h, 4 h, 6 h in MCI-154 + NS treated group were significantly higher than those in NS treated group. Hence, it is indicated that the possible negative effect of MCI-154 on systemic blood pressure can be counteracted by adequate fluid infusion.

In summary, our study showed that MCI-154, a calcium sensitizer, exerted significantly therapeutic effects on cardiac dysfunction after endotoxic shock in rabbits, suggesting that MCI-154 may improve cardiovascular function by means of increasing Ca^{2+} sensitivity of the cardiac contractile apparatus even under the condition of sepsis/septic shock. We find these results encouraging and believe that MCI-154 may be a promising positive inotropic agent for the treatment of endotoxic shock.

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钙增敏剂 MCI-154 对内毒素血症家兔心功能的影响[1]

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关键词 心脏；内毒素类；左心室功能；内毒素血症；强心药；钙；MCI-154

目的：研究钙增敏剂 MCI-154 对内毒素血症家兔心功能的影响. **方法**：内毒素血症家兔静脉注射 MCI-154 1.0 mg·kg^{-1}，然后再输入 50 mL·kg^{-1}生理盐水(NS) + MCI-154 0.1 mg·kg^{-1}液体. 监测心功能指标. **结果**：单纯给予 50 mL·kg^{-1} NS 治疗，对内毒素血症家兔心功能无明显改善作用. MCI-154 + NS 治疗后，左室收缩压(LVSP)、左室等容收缩压(IP)、心肌收缩性能(MC)、心肌收缩向量环面积(Lo)明显增加，显著高于单纯 NS 治疗组. MCI-154 治疗后，心率(HR)无明显增加，左室舒张末压(LVEDP)明显降低. **结论**：钙增敏剂 MCI-154 对家兔内毒素血症心功能障碍具有良好的治疗效果.

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