

Energetic Advantage of Phosphodiesterase III Inhibitors in the Failed Heart after Global Ischemia

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We evaluated the ventricular mechanical effects of Phosphodiesterase III (PDE III) inhibitors in the failed heart after global ischemia induced by ventricular fibrillation (VF) using the left ventricular pressure-volume relationship (PVR). In 14 anesthetized open-chest dogs, left ventricular PVR was measured using a conductance catheter. Under administration of milrinone (MIL, n=7) and olprinone (OLP, n=7), the slopes of the LV end-systolic pressure-volume (E_{max}), arterial end-systolic pressure-stroke volume relations (E_a), ventriculoarterial coupling (E_a/E_{max}) and preload recruitable stroke work (PRSW) were obtained to evaluate changes in LV performance. The duration of VF was 1 min without cardiopulmonary bypass (CPB). OLP and MIL significantly increased the E_{max} and PRSW values in the failed heart after VF, and there was no dose-effect relationship at MIL doses of 0.25 to 0.75 $\mu\text{g}/\text{kg}/\text{min}$ or at OLP doses of 0.1 to 0.3 $\mu\text{g}/\text{kg}/\text{min}$. The E_a/E_{max} value after VF was significantly lower in the presence of OLP or MIL than in the absence of these drugs (-45.3% with OLP and -46.5% with MIL). The results indicate that in the heart after transient global ischemia, both OLP and MIL improve hemodynamic and mechanical states in terms of ventriculoarterial coupling.

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Introduction

Left ventricular function has recently been assessed by the conductance catheter method, which measures the left ventricular end systolic pressure-volume relation-

ship (ESPVR). Several experimental studies have found that analyzing ventriculoarterial coupling using the time-varying elastance model is useful in evaluating the relationship between ventricular contractility and arterial afterload as energetic assessment^(1–4), and the method has been implemented in several types of study^(5, 6). Phosphodiesterase III (PDE III) inhibitor, catecholamines and calcium sensitizing agents have been assessed in diseased human hearts^(7–10). Furthermore, several studies have analyzed the influence of ventricular fibrillation (VF) on postfibrillatory cardiac function^(11, 12), but few studies have assessed global ischemia induced by VF without cardiopulmonary bypass (CPB), that is the novel condition of the present study compared with previous studies. The first purpose of this study is to evaluate left ventricular hemodynamic and mechanical effects of PDE III inhibitors in the failed heart after global ischemia induced by VF from the view point of ventriculoarterial coupling analyzed with left ventricular pressure-volume relationship (PVR). The second purpose of this study is to compare olprinone (OLP) and milrinone (MIL) in terms of hemodynamic and mechanical efficacies after the transient global ischemia.

Materials and Methods

Preparation of animals

All experimental procedures and protocols described in this study were approved by the Animal Care and Use Committee of Nagasaki University School of Medicine. Fourteen adult mongrel dogs with a mean weight of $11.4 \pm 2.9\text{kg}$ were premedicated with a subcutaneous injection of ketamine hydrochloride (10 mg/kg) and anesthetized with intravenous sodium pentobarbital (25mg/kg). Small supplemental doses of sodium pentobarbital were administered to each dog to keep stable hemodynamics and oxygenation, in which blood pressure, heart rate (HR), and arterial blood gases were monitored. Under anesthesia, dogs were

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intubated and ventilated by a mechanical ventilator with intermittent positive pressure in the supine position. The mean respiratory rate was maintained at 14 breaths per minute and tidal volume was adjusted to 20ml/kg. The arterial pH, P_{O_2} , and P_{CO_2} were maintained within their physiological ranges. A midline sternotomy was performed in the supine position and the heart was suspended in a pericardial cradle. To measure left ventricular pressure a micromanometer-tipped catheter (Model MPC-500, 5F, Millar Instruments, USA) was inserted from the left ventricular apex. A conductance catheter (ANP-455, 7F, Leycom, Netherlands) was also inserted into the left ventricular apex to measure left ventricular volume. These catheters were positioned parallel to the long axis of the left ventricle. A drug infusion line was placed at the base of pulmonary artery, and snaring tape was placed around the inferior vena cava (IVC) to change the preload. Before starting the experiment, a bolus injection of hypertonic saline solution (5% NaCl) into the pulmonary artery was induced to calibrate conductance of the surrounding tissues⁽¹³⁾. Left ventricular PVR was simultaneously obtained by a conductance catheter attached to a stimulator/processor (Sigma-5, Leycom, Netherlands) via the micromanometer-tipped catheter.

Experimental protocol

The animals were divided into two groups, one of which was given milrinone (MIL; n=7) and the other received olprinone (OLP; n=7). The administration rate of the PDE III inhibitor was regulated appropriately based on clinical doses. At first in both groups PVR was obtained by transient IVC snaring for 10 seconds to reduce preload under the end-expiratory phase with no medication. Thereafter, VF was electrically induced by a direct current wave of 24v (0.5A). The heart was maintained in a state of fibrillation for 1 min, and then cardiac beating was restored with a direct current shock of 10 Joules. After 1min, PVR was obtained by the same procedure. Over the next 30 min, the heart was kept beating without medication, after the parallel conductance was re-checked a control PVR value was measured before drug administration. In the MIL group, MIL was first administered at 50 $\mu\text{g}/\text{kg}$ for 10 min as a loading dose. Thereafter, MIL was administered at a rate of 0.25 $\mu\text{g}/\text{kg}/\text{min}$ continuously for 20 min and PVR was measured. In the same fashion, PVR values were obtained at dose rates of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ and 0.75 $\mu\text{g}/\text{kg}/\text{min}$. Under a continuous infusion of MIL at a rate of 0.75 $\mu\text{g}/\text{kg}/\text{min}$, VF was induced using the same method. The heart was kept fibrillated for 1 min and restored with direct current

shock. After 1 min, PVR was obtained in the same manner. In the OLP group, OLP was first administered at 10 $\mu\text{g}/\text{kg}$ for 5 min as a loading dose. Thereafter, OLP was administered at a rate of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ for 20 min and PVR was measured. In the same manner PVR values were obtained at rates of 0.2 $\mu\text{g}/\text{kg}/\text{min}$ and 0.3 $\mu\text{g}/\text{kg}/\text{min}$. The measurement of PVR after second VF was done during a continuous infusion of OLP at a rate of 0.3 $\mu\text{g}/\text{kg}/\text{min}$ as described for the MIL group.

Analysis of left ventricular pressure-volume relationship

To evaluate changes in LV performance, the slopes of the LV end-systolic pressure-volume (E_{max}), arterial end-systolic pressure-stroke volume relationship (E_a), ventriculoarterial coupling (E_a/E_{max}) and preload recruitable stroke work (PRSW) were obtained by the conductance catheter method. Pressure-volume loops were recorded during 10-second caval snaring as the sequence of beats following left ventricular preload reduction (Fig.1). The left ventricular PVR during preload reduction was fitted using linear regression analysis to:

$$\text{ESP} = E_{\text{max}} (\text{ESV} - V_0),$$

where ESP is the end-systolic pressure, ESV is the end-systolic volume, V_0 is the volume axis intercept of the ESPVR and E_{max} is the load-independent contractile index. The value of E_a , which is the slope of end-systolic pressure-stroke volume relationship represents arterial load as an effective arterial chamber related to

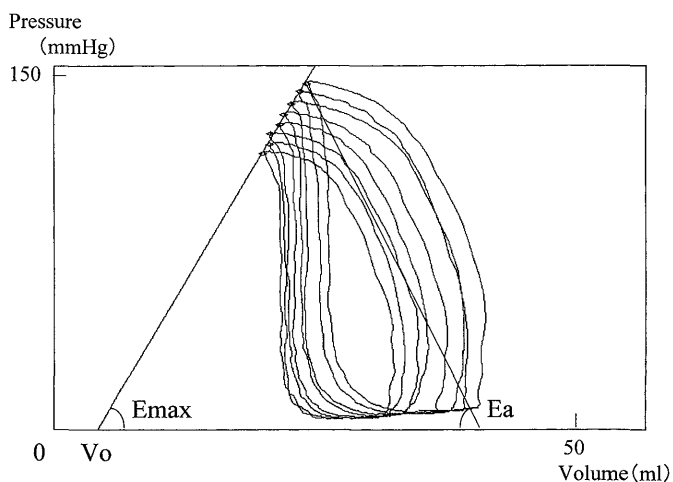


Fig. 1. Representative pressure-volume loops obtained by conductance catheter methods during caval snaring and diagram showing E_{max} , E_a and V_0 . E_{max} ; slope of LV end-systolic pressure-volume relationship, V_0 ; the volume intercept of end-systolic pressure-volume relationship, E_a ; negative value of diagonal line connecting end-systolic pressure-volume point and end-diastolic point on volume axis.

the Windkessel parameters of the arterial system. Thus,

$$E_a = \text{ESP} / \text{SV},$$

where E_a is the negative value of the slope of the diagonal line connecting the end-systolic pressure-volume point and the end-diastolic point on the volume axis (Fig.1). The ratio E_a / E_{max} represents ventriculoarterial coupling. When effective arterial elastance equals ventricular elastance, that is, when $E_a / E_{\text{max}} = 1$, stroke work (SW) should be maximized because SW is expressed as:

$$\text{SW} = \text{ESP} \times \text{SV} = E_a \times (\text{EDV} - V_o)^2 / (1 + E_{\text{max}} / E_a)^2,$$

where EDV is the end-diastolic volume and SV is stroke volume. In this manner, energetic effects were determined by ventriculoarterial coupling⁽¹⁻³⁾. Canine experiments have shown that the left ventricle performs maximal external work relative to the arterial load when the ventricular and arterial elastance are equalized⁽²⁾. As other measure of the LV contractile state, PRSW is generally accepted as the load-insensitive contractile index, namely, the linear relationship between LV stroke work and end-diastolic volume^(1,14,15).

Statistics

End-systolic PVR was obtained using linear regression analysis. All data are reported as means \pm standard deviation (SD). Repeated measures ANOVA compared E_{max} , E_a , E_a / E_{max} , RRSW, HR and ESP. When repeated measures ANOVA revealed significant differences according to the F test, matched pairs before and after administration of MIL or OLP were compared by a two-tailed paired t test. To compare the mean of variables in the MIL group and OLP group, a two-tailed unpaired t test was applied. A p value of < 0.05 was taken to indicate a significant difference.

Results

Baseline hemodynamics and conditions

Body weight (BW), HR, end-systolic pressure (ESP), E_{max} , E_a , E_a / E_{max} , PRSW, and V_o did not significantly differ between the OLP and MIL groups without medication before inducing VF as experimental control conditions.

Dose-effect relations in the presence of OLP and MIL

In the MIL and OLP groups, repeated measures ANOVA detected time-related significant changes

within each group throughout whole study. Time related differences in HR, ESP, E_{max} , E_a , E_a / E_{max} and PRSW in the OLP group were significant. In the MIL group, there were no significant differences in HR or ESP. Figure 2 shows dose-effect relations in the HR of the two groups. In each group, there were no significant differences between several experimental states. In addition, at the same state there was no significant difference between MIL and OLP groups. Figure 3 shows dose-effect relations in the ESP of the two groups. After beating was restored from the initial fibrillated state ESP tended to decrease with administration of PDEIII inhibitors, but there were no significant differences between several experimental states in each groups. Figure 4 shows dose-effect relations in the E_{max} values of the two groups. At VF30 state, E_{max} did not significantly differ from the baseline state in both groups. After starting the administration of PDE III inhibitors, E_{max} values maximally increased to 17.4

HR

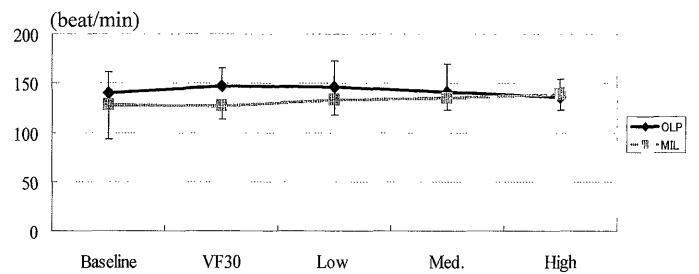


Fig. 2. Changes of HR in the OLP and MIL groups. Baseline; control state before VF with no medication, VF30; restored beating state after 30min from VF with no medication, Low; state just after administration at a rate of low dose for 20min (OLP; $0.1 \mu\text{g}/\text{kg}/\text{min}$, MIL; $0.25 \mu\text{g}/\text{kg}/\text{min}$), Med.; state just after administration at a rate of medium dose for 20min (OLP; $0.2 \mu\text{g}/\text{kg}/\text{min}$, MIL; $0.50 \mu\text{g}/\text{kg}/\text{min}$), High; state just after administration at a rate of high dose for 20min (OLP; $0.3 \mu\text{g}/\text{kg}/\text{min}$, MIL; $0.75 \mu\text{g}/\text{kg}/\text{min}$).

In each group, there was no significant difference at the point of dose-effect relation.

SBP

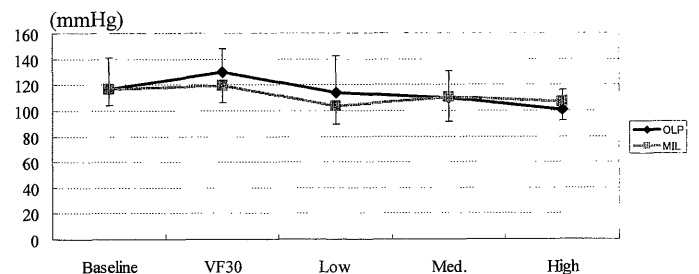


Fig. 3. Changes of ESP in the OLP and MIL groups. Experimental states were as described in Figure 2. In each group, there was no significant difference at the point of dose-effect relation.

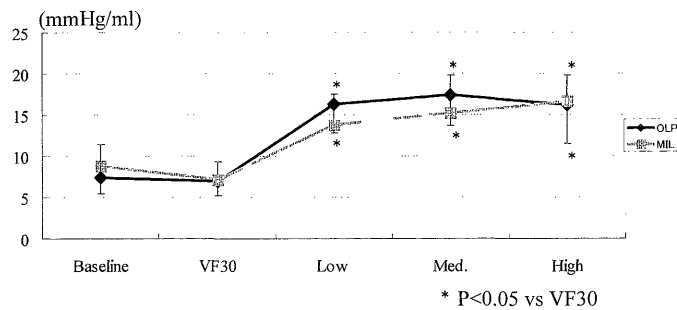
E_{max}

Fig. 4. Changes of E_{max} in the OLP and MIL groups. Experimental states were as described in Figure 2. In each group, there were significant differences between administrating states and VF30 state at the point of dose-effect relation.

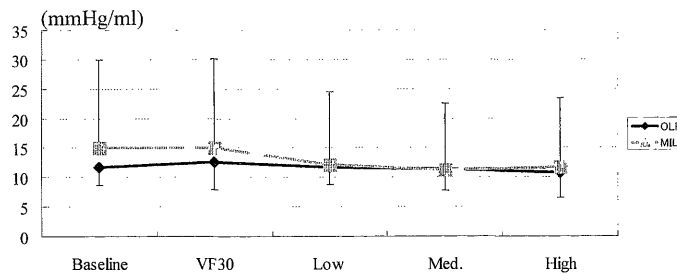
E_a

Fig. 5. Changes of E_a in the OLP and MIL groups. Experimental states were as described in Figure 2. In each group, there was no significant difference at the point of dose-effect relation.

± 3.71 mmHg/ml in the OLP group, and to 16.6 ± 3.16 mmHg/ml in the MIL group. These changes were significant compared to VF30 state at each administrating states. Figure 5 shows dose-effect relations in the E_a value of the two groups. The administration of OLP and MIL resulted in similar decreases in both groups, but there were no significant differences between several experimental states in each groups. Figure 6 shows dose-effect relations in the values of ventriculoarterial coupling (E_a/E_{max}) of the two groups. There were no significant differences between baseline state and VF30 state in both groups (+10.4%, $p=0.25$ in the OLP group and +23.7%, $p=0.27$ in the MIL group). When a stable contractile state was attained after beating was restored from the initial fibrillated state with no medication, E_a/E_{max} maximally increased in both groups. However the values of E_a/E_{max} decreased to 0.69 ± 0.29 in the OLP group (-72.1%), and 0.73 ± 0.33 in the MIL group (-66%) under the continuous administration of OLP or MIL, respectively. Compared to VF30 state, there were significant differences between several experimental states in each groups. In addition during the entire experimental course E_a/E_{max} did not

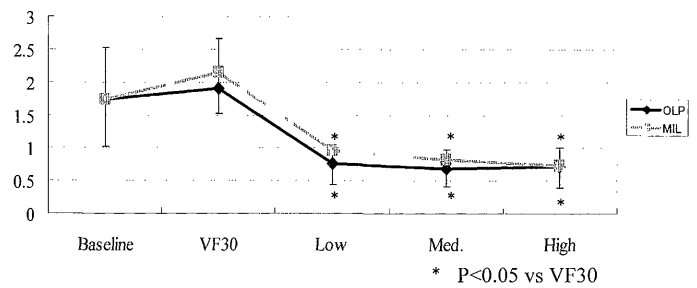
E_a/E_{max}

Fig. 6. Changes of E_a/E_{max} in the OLP and MIL groups. Experimental states were as described in Figure 2. In each group, there were significant differences between administrating states and VF30 state at the point of dose-effect relation.

PRSW

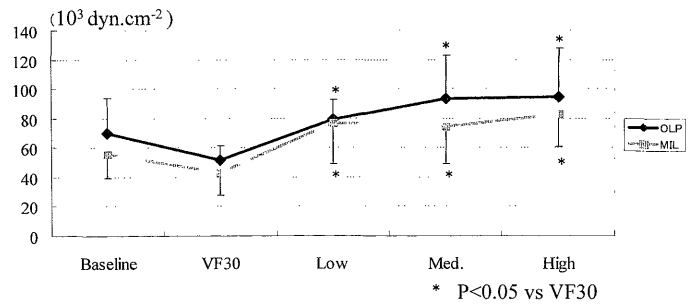


Fig. 7. Changes of PRSW in the OLP and MIL groups. Experimental states were as described in Figure 2. In each group, there were significant differences between administrating states and VF30 state at the point of dose-effect relation.

statistically differ between the OLP and MIL groups. Figure 7 shows dose-effect relations in the PRSW value of the two groups. The administration of OLP or MIL resulted in similar changes in PRSW compared with those of E_{max}. There were significant differences between administrating states and VF30 states in each groups. Effects of OLP and MIL on hemodynamics in VF-induced failed hearts were summarized in Table 1 and 2. At restored beating state from the VF with continuous high dose administration of OLP, the value of E_a/E_{max} was significantly lower compared to restored beating state from the VF with no drug (-45.3%, $p=0.028$). In MIL group, E_{max} was higher and the value of E_a/E_{max} was lower (-46.5%, $p=0.01$) significantly compared to restored beating state from the VF with no drug. As compared with OLP group, the value of E_{max} of MIL group was significantly higher in the restored beating state from the VF with continuous high dose administration. In other values, there was no significant difference between two groups.

Table 1. Effects of OLP on the hemodynamics after VF Baseline; control state before VF with no medication, No drug after VF; restored beating state after 1min from VF with no medication; OLP after VF; restored beating state after 1min from second VF under continuous administration at a rate of 0.3 $\mu\text{g}/\text{kg}/\text{min}$.

	Baseline	After VF	
		No drug	OLP
HR (bpm)	140 \pm 21.5	139 \pm 22.6	128 \pm 19.7
ESP(mmHg)	116 \pm 24.8	128 \pm 21.2	113 \pm 10.2
E _{max} (mmHg/ml)	7.46 \pm 2.04	5.53 \pm 2.94	6.70 \pm 0.95 §
E _a (mmHg/ml)	11.7 \pm 3.10	11.8 \pm 3.94	8.91 \pm 1.88
E _a /E _{max}	1.74 \pm 0.80	2.47 \pm 0.80	1.36 \pm 0.36 *
PRSW (10 ³ dyn.cm ⁻²)	69.8 \pm 24.1	51.9 \pm 14.9	86.8 \pm 47.6

* P<0.05 vs no drug

§ P<0.05 vs MIL(Table 2)

Table 2. Effects of MIL on the hemodynamics after VF Baseline; control state before VF with no medication, No drug after VF; restored beating state after 1min from VF with no medication; MIL after VF; restored beating state after 1min from second VF under continuous administration at a rate of 0.75 $\mu\text{g}/\text{kg}/\text{min}$.

	Baseline	After VF	
		No drug	MIL
HR (bpm)	128 \pm 34.8	124 \pm 21.2	132 \pm 13.3
ESP(mmHg)	117 \pm 12.9	112 \pm 15.1	110 \pm 17.0
E _{max} (mmHg/ml)	8.85 \pm 2.54	6.23 \pm 1.76	9.76 \pm 2.31 *,§
E _a (mmHg/ml)	15.0 \pm 5.70	13.0 \pm 4.79	10.7 \pm 3.67
E _a /E _{max}	1.73 \pm 0.71	2.15 \pm 0.71	1.15 \pm 0.53 *
PRSW (10 ³ dyn.cm ⁻²)	55.9 \pm 16.3	50.9 \pm 19.2	71.9 \pm 30.7

* P<0.05 vs no drug

§ P<0.05 vs OLP (Table 1)

Discussion

Congestive heart failure has recently been clinically treated with PDE III inhibitors⁽¹⁶⁾, which confer the benefits of augmented cardiac output and reduced ventricular filling pressure. The PDE III inhibitors have positive inotropic effects on the heart and vasodilating activities. The effect of PDE III inhibitor is mediated by the inhibition of selective PDE III isoenzymes with an increase in cyclic adenosine monophosphate. Cytosolic free Ca is thought to be increased via a cascade of reactions in the heart resulting in increased contractility. On the other hand, cytosolic free Ca of vascular smooth muscle cells is thought to be decreased resulting in vasodilatation, which manifests as a significantly increased distensibility of the carotid arteries after the administration of PDE III inhibitor⁽¹⁷⁾.

The effectiveness of PDE III inhibitor on ventriculoarterial coupling and myocardial energetics has been shown in the diseased human heart⁽¹⁰⁾. In that study PDE III

inhibitor improved ventriculoarterial coupling more than dobutamine, with a resultant increase in mechanical efficiency. Another study showed that E_{max} increased to the same extent with dobutamine, PDE III inhibitor and Ca sensitizing agent and that E_a was unchanged with dobutamine or Ca sensitizing agent, but decreased with PDE III inhibitor. Thus E_a/E_{max} was decreased by all inotropic agents but to the greatest extent by PDE III inhibitor⁽⁸⁾. In this ventriculoarterial coupling, the arterial system is treated as if the elastic chamber has volume elastance E_a just as the left ventricle is treated as an elastic chamber with end-systolic elastance E_{max}⁽¹⁾. In this sense, ventriculoarterial coupling represents the function of both the ventricle and the arterial system, so it is reasonable to evaluate PDE III inhibitor which affects both the ventricle and the arterial system from the viewpoint of ventriculoarterial coupling.

Several studies have analyzed human hearts with local ischemia due to myocardial infarction^(9,10). Furthermore, several studies have assessed whole ischemic hearts induced by VF under CPB. One such study showed that VF for 20 to 40 min does not depress postfibrillatory contractility when normal coronary blood perfusion is maintained in the canine left ventricle⁽¹¹⁾. Another study showed that a short duration of spontaneous VF during CPB might induce subendocardial ischemic damage at lower perfusion pressures (30 and 60mmHg). On the other hand, the empty beating heart does not induce subendocardial underperfusion at such low perfusion pressures⁽¹²⁾.

We induced ventricular global ischemia in the present study using VF without CPB to evaluate left ventricular mechanical effects in terms of ventriculoarterial coupling. It was easy and steady method to get the transient global ischemic state by inducing VF for 1min without CPB, so post VF period was chosen as the experimental setting. Furthermore these situations are not demonstrated in clinical settings but proofed under local ischemia in clinical cases as myocardial infarction^(9,10). As experimental studies there were few studies under global ischemia, it was important to measure E_a/E_{max} to clear the effect of PDE III inhibitors under these settings. The results of this study indicate that PDE III inhibitors improve hemodynamic and mechanical effects in the heart after VF-induced brief global ischemia without CPB. At the point of postfibrillatory left ventricular load-independent contractility, OLP or MIL similarly increased the values of E_{max} and PRSW. Yet another study indicated that PRSW may be a more linear and reliable index with which to evaluate contractility in man⁽¹⁵⁾, but the present study found no significant differences between the values of E_{max} and

PRSW. In this study OLP and MIL similarly increased the E_{\max} and PRSW values in a dose-independent manner. The E_a values tended to decrease with no significance, and the values of E_a/E_{\max} significantly decreased in the VF-induced failed hearts.

In conclusion, PDEIII inhibitors improve hemodynamic and mechanical states in the heart after transient global ischemia induced by VF in terms of ventriculoarterial coupling.

Acknowledgments

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