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Effects of pretreatment with cardiostimulants and beta-blockers on isoprenaline-induced takotsubo-like cardiac dysfunction in rats

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ABSTRACT

Background: Takotsubo syndrome (TS) is an acute cardiac syndrome characterized by regional myocardial akinesia that is not caused by coronary artery occlusion. Exogenous as well as endogenous excess catecholamines can induce TS. The aim of this study was to explore the effects of pharmacological cardio-simulative and cardio-depressing drugs on the development of isoprenaline-induced takotsubo-like cardiac dysfunction, a rat model of TS.

Methods: We randomized 295 rats into twelve groups. The animals were randomized to pre-treatment with either a low or high dose of metoprolol, propranolol, ICI 118551 (beta$_2$-receptor antagonists), milrinone (phosphodiesterase inhibitor), levosimendan or saline (control) before induction of TS with isoprenaline. In one additional group, high dose of milrinone was administered alone. We measured invasively blood pressure and heart rate over a period of 90 min. Cardiac function and morphology were evaluated with high-resolution echocardiography.

Results: Milrinone alone induced apical ballooning similar to isoprenaline. Pretreatment with propranolol and metoprolol but not with ICI 118551 attenuated takotsubo-like akinesia in a dose-dependent manner. Pretreatment with metoprolol decreased mortality. Pretreatment with levosimendan resulted in higher incidence of apical ballooning while pretreatment with milrinone did not change the degree of akinesia.

Conclusion: The phosphodiesterase inhibitor milrinone induces takotsubo-like dysfunction in the absence of exogenous catecholamines. This finding challenges the concept that high levels of circulating catecholamines or excessive stimulation of adrenergic receptors are necessary for the development of takotsubo syndrome. Our study provides experimental evidence for the concept of avoidance of inotropes and that selective beta$_1$-blockade may be beneficial in the treatment of TS-patients.

1. Introduction

Takotsubo syndrome (TS) is an acute cardiac syndrome with a clinical course similar to acute myocardial infarction. However, in TS, ventricular dysfunction does not follow coronary artery territories and is not caused by occlusion of a coronary artery. Instead, physical or emotional stress can trigger TS. The typical form of TS is characterized by apical akinesia and basal hyperkinesia—a phenotype that resolves within days or weeks [1–5]. TS was considered to have an excellent prognosis, but recent studies showed that short- and long-term mortality in TS is similar to myocardial infarction [5,6]. Currently, there is no specific treatment for TS that is based on randomized clinical trials.

Even if the evidence that physical or emotional stress with concomitant catecholamines excess are involved in the pathogenesis of TS is relatively strong, the more detailed mechanisms are not known [3–5]. It has been postulated that stimulation of beta-adrenergic receptors is important for the development of TS [8–11]. However, it has not been tested whether beta-adrenergic receptors are necessary for the development of TS and how the inotropic state of myocardium affects left ventricular function and morphology in TS. We have previously established a rat model that mimics the most important clinical characteristics of TS in humans [8]. The results from our model were reproduced independently by others [12].

The aim of this study was to evaluate how pretreatment with cardiostimulative and cardiodepressing pharmacological agents

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influence the development of isoprenaline-induced takotsubo-like cardiac dysfunction in rats and whether takotsubo-like phenotype could be induced pharmacologically without direct stimulation of beta-adrenergic receptors.

2. Methods

Ethical Committee at Gothenburg University for animal studies approved the experimental protocol. We followed the NIH guidelines for experimental animal use. A total number of 295 Sprague-Dawley male rats were used. The animals were housed in a temperature-controlled environment (25 °C) with 12 h light/dark cycle and free access to food and water. Aiming to study whether cardiostimulant or cardiodepressive agents could prevent or enhance isoprenaline-induced takotsubo-like cardiac dysfunction, we randomized the rats into twelve groups (Fig. 1). We used 175 animals for non-invasive evaluation of cardiac function and morphology, and 120 animals for invasive evaluation of hemodynamic profile. Ketamine (50 mg/kg IP) and midazolam (5 mg/kg IP) were used as anesthesia. The rats were anesthetized to allow echocardiographic evaluation of left ventricular function and morphology and continuous invasive hemodynamic monitoring. This particular regimen for general anesthesia does not affect the development of takotsubo-like cardiac dysfunction in this model [12]. We removed hair on the neck and chest. The animals were then placed in supine position on a heating pad to preserve the body temperature at 38 ± 0.2 °C for at least 10 min. These settings were maintained during the entire experiment. The right common carotid artery was freely dissected and cannulated for continuous monitoring of blood pressure and heart rate. The rats received additional boluses of ketamine and midazolam when needed during the entire duration of the experiment.

2.1. Study protocol

This study is based on a rat model of isoprenaline-induced takotsubo-like dysfunction that was previously introduced by our group [8], and independently validated by others. In these experiments, we pretreated the rats with either beta blockers or non-catecholamine positive inotropic agents as outlined in Supplemental Fig. 1. The rats were randomized to pretreatment with an intraperitoneal bolus of one of the following substances: saline (CTRL), metoprolol (selective $beta_1$-receptor blocker) 5 mg/kg (MET 5), metoprolol 50 mg/kg (MET 50), propranolol (non-selective beta-receptor blocker) 2.5 mg/kg (PROP 2.5), propranolol 25 mg/kg (PROP 25), ICI 118551 hydrochloride (selective $beta_2$-receptor blocker) 5 mg/kg (ICI 5), ICI 12 mg/kg (ICI 12), levosimendan (calcium sensitizer and phosphodiesterase inhibitor) 10 μg/kg (LEVO 10), levosimendan, 50 μg/kg (LEVO 50), milrinone (phosphodiesterase inhibitor) 50 μg/kg (MIL 50) or milrinone 250 μg/kg (MIL 250). Thereafter, all rats received an intraperitoneal bolus of isoprenaline 50 mg/kg. A separate group of rats received milrinone 25 mg/kg only (MIL-X). Each group consisted of twelve rats in the non-invasive experiments and six rats in the invasive experiments. To study the dose-response effects, each drug was given in a lower and higher dose. Ten minutes after injection of the drug, each rat received isoprenaline 50 mg/kg except the group that received 25 mg/kg milrinone. We administered milrinone without isoprenaline to evaluate whether takotsubo-like dysfunction can be induced in rats in the absence of exogenous catecholamines. This group received saline instead of isoprenaline. All investigators were blinded to treatment assignment during the evaluation.

Evaluation of left ventricular function and morphology with transthoracic echocardiography.

Ninety minutes after isoprenaline injection, we performed echocardiography with the use of 770 VEVO imaging machine which has an integrated rail system for adjustment of the ultrasound probe. For imaging, we used a 35 MHz linear transducer (RMV 707). We acquired a long axis view with visualization of aortic and mitral valves and maximum length of LV cavity (LAX view). With the help of ECG-gated kilohertz visualization technique, a cine loop of >1000 frames was obtained. The akinetic area was traced in the long axis view, along the endocardial border of the left ventricle, and expressed as a percentage of total LV endocardial length. Cardiac function was estimated using fractional area change as follows: FS = (EDA-ESA)/EDA, where EDA is end-diastolic area and ESA is the end-systolic area. Takotsubo-like cardiac dysfunction was defined as >20% akinesia in the LV.

Invasive hemodynamics.

We evaluated blood pressure and heart rate invasively with rats under general anesthesia with ketamine and midazolam. We dissected free right common carotid artery and inserted a cannula connected through pressure sensor to (Pharmlab Astra Zeneca, Möndal, Sweden.). We recorded continuously blood pressure and pulse rate over a period of 90 min. The rats were kept under general anesthesia during the whole period. After the invasive evaluation of hemodynamics, the rats were kept under anesthesia and were immediately assessed by transthoracic echocardiography. The rats were sacrificed at the end of these procedures.

2.2. Statistics

All variables were tested for normal distribution with Shapiro-Wilks test and by inspection of histograms. For comparison of incidences between groups with binary variables, we used Fischer's exact test. For comparison between groups with continuous, normally distributed variables, we used ANOVA with post hoc Fisher's LSD (least square significance) test. For comparison between groups with continuous, non-normally distributed data, we used Kruskal-Wallis with Mann-Whitney *U* test. For evaluation of a dose-dependent effect of different drugs on the degree of akinesia, we used Jockhere-Tempesta test for trend. A *p*-value <0.05 was considered significant. For evaluation of changes over time in heart rate and arterial blood pressure, we used a linear mixed model with an autoregressive covariance matrix. We calculated AUC (area under the curve) for heart rate, blood pressure, and rate-pressure product. We used linear regression to evaluate the association between the extent of akinesia and heart rate, blood pressure and rate-pressure product. All analyses were performed with Stata software (release 14.1, Stata Corporation 2016).

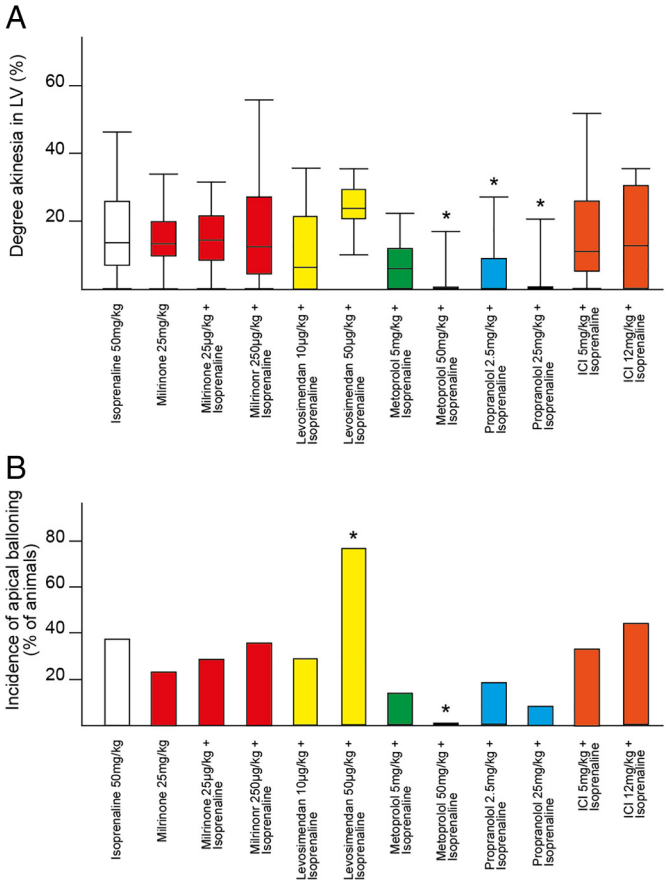

Fig. 1. Degree of left ventricular akinesia and incidence of apical ballooning. The degree of akinesia in the left ventricle (A) and incidence of apical ballooning (B) in the different groups. * $p < 0.05$ vs group Isoprenaline 50 mg/kg.

3. Results

3.1. Left ventricular function and morphology

Median degree of akinesia in the control group was 13.4% (IQR 6.7–25.7). Takotsubo-like apical ballooning (akinesia of >20% of left ventricle) was observed in 37.0% of these rats (Figs. 1, 2 and Supplemental video 1). Rats treated with high dose of levosimendan (LEVO 50) had a significantly higher incidence of apical ballooning (76.9%; $p = 0.041$ vs. control). The incidence of akinesia and apical ballooning was similar in rats pretreated with low dose of levosimendan, low dose and high dose milrinone and in the control group (Fig. 1 and Supplemental video 2). Pretreatment with high dose metoprolol and propranolol reduced the extent of apical akinesia (median 0%, IQR 0.0–0.0 for MET 50 and median 0%, IQR 0.0–0.0 for PROP 25; both $p < 0.001$ vs. CTRL) and abolished development of takotsubo-like apical ballooning (Supplemental video 3). Almost none of the rats that were pretreated with these agents developed akinesia. When metoprolol and propranolol were administered in lower doses (MET 5 and PROP 2.5), we observed a non-significant reduction in the extent of apical akinesia (Fig. 1). We found a strong dose-dependent effect

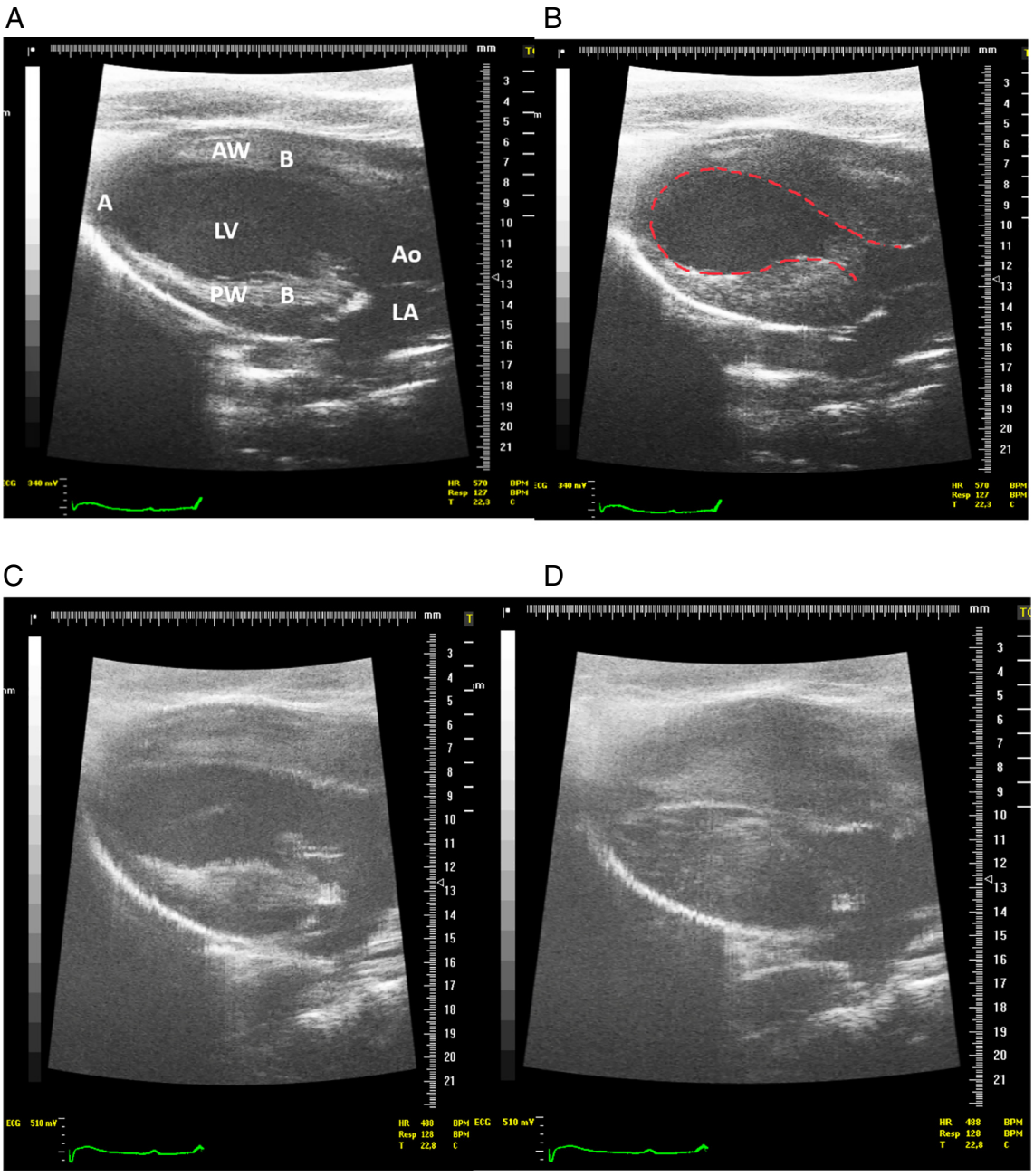

Fig. 2. Echocardiography images of isoprenaline-induced takotsubo-like left ventricular apical akinesia. Upper panel: Echocardiographic images after induction of isoprenaline-induced takotsubo-like apical dysfunction, at end-diastole (A) and end-systole (B); showing apical ballooning in systole, as indicated by the dotted red line (tracing of the endocardium). Lower panel: Echocardiographic images of a normally contracting rat heart, at end-diastole (C) and end-systole (D).

for pretreatment with metoprolol ($p < 0.001$) and propranolol ($p < 0.001$) with decreasing extent of akinesia in apical segments. On the other hand, pretreatment with other pharmacological agents did not reduce the degree of akinesia. Pretreatment with beta$_2$-receptor antagonist, ICI 118551, did not affect the incidence of takotsubo-like dysfunction in lower (ICI 5) as well as in higher dose (ICI 12) (Fig. 1). Milrinone administered alone (MIL-X) induced takotsubo-like cardiac dysfunction in 21% of the rats [median degree of akinesia 13.2% (IQR 9.5–19.7), $p = 0.75$ vs. control; Fig. 1, and Supplemental video 1]. Compared to the control group, stroke volume was significantly higher in the rats pretreated with both low and high dose metoprolol, while ejection fraction was significantly higher only in the high dose metoprolol group (Supplemental Table). There was no difference in stroke volume and ejection fraction between all the other groups and the control group. Left ventricular volume in diastole was highest in the high dose metoprolol group.

3.2. Hemodynamics

We found no difference between the groups in heart rate, systolic and diastolic blood pressure at baseline (Table 1). After administration of isoprenaline, heart rate increased by 67% in the control group (ISO) from ~400 to ~600 beats per minute over the first 30 min and remained at that level for the remaining duration of the experiment (Fig. 3). Compared to the control group (ISO), heart rate was significantly lower both

Table 1
Left ventricular function and morphology evaluated by transthoracic echocardiography at 90 min after administration of experimental treatment.

Group	N	BW (g)	EDV (μl)	ESV (μl)	EF (%)	SV (μl)
Isoprenaline 50 mg/kg	26	300	260 ± 106	77 ± 48	69 ± 17	157 ± 117
Milrinone 50 μg/kg	16	304	248 ± 115	88 ± 69	65 ± 15	161 ± 84
Milrinone 250 μg/kg	14	299	296 ± 96	90 ± 58	67 ± 22	206 ± 105
Levosimendan 10 μg/kg	15	303	270 ± 76	82 ± 75	77 ± 21	200 ± 69
Levosimendan 50 μg/kg	16	307	288 ± 60	125 ± 51	57 ± 17	163 ± 52
Metoprolol 5 mg/kg	17	308	318 ± 102	101 ± 105	72 ± 20	217 ± 72*
Metoprolol 50 mg/kg	18	301	329 ± 103*	60 ± 44	83 ± 9*	269 ± 74*
ICI118551 5 mg/kg	15	306	272 ± 13	105 ± 92	65 ± 20	167 ± 63
ICI118551 12 mg/kg	15	295	258 ± 117	122 ± 89	57 ± 17	136 ± 54
Propranolol 2,5 mg/kg	16	302	290 ± 139	115 ± 118	68 ± 25	174 ± 79
Propranolol 25 mg/kg	17	300	297 ± 89	66 ± 44	77 ± 15	209 ± 106
Milrinone alone 25 mg/kg	12	322	275 ± 86	107 ± 63	63 ± 14	168 ± 49

BW = body weight; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; SV = stroke volume. *$p < 0.05$ vs Isoprenaline 50 mg/kg.

in the milrinone and metoprolol groups (Fig. 3). Metoprolol induced a dose-dependent negative chronotropic effect. There was no difference in heart rate between the control (ISO) and any other group (Fig. 3). Systolic blood pressure was lower in the milrinone group but not in the other groups compared to the control group (ISO) (Supplemental Fig. 2). Using curve-fitting of data with linear regression based on all

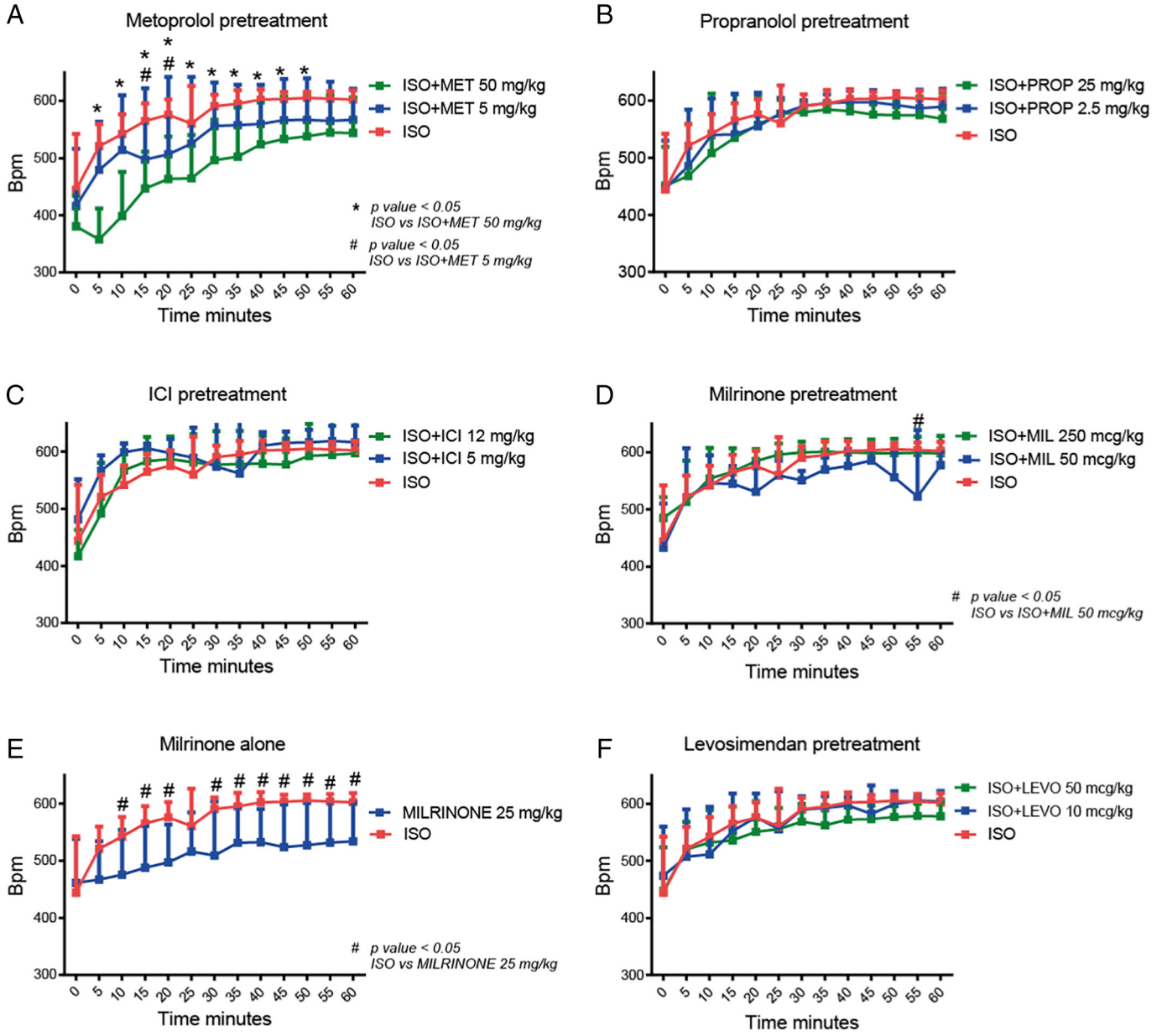

Fig. 3. Heart rate. Heart rate in animals pretreated with high or low dose of metoprolol (A), propranolol (B), ICI (C), milrinone (D), levosimendan (F) or high dose milrinone alone (E). ISO = isoprenaline; MET = metoprolol; PROP = propranolol; ICI = ICI 118551 hydrochloride; MIL = milrinone; LEVO = levosimendan.

observations, we found that the extent of akinesia was strongly associated (beta coefficient 0.531, 95% CI 0.191–0.869, $p = 0.003$) with heart rate (Supplemental Fig. 3A). This association was weaker (beta coefficient 0.028, 95% CI −0.0029–0.059, $p = 0.075$) for rate * pressure product (Supplemental Fig. 3B). We found no association between the extent of akinesia and blood pressure (beta coefficient 0.136, 95% CI −0.068–0.340, $p = 0.188$).

3.3. Mortality

Mortality was 33% in control group (isoprenaline 50 mg/kg) (Supplemental Fig. 4). Death was significantly lower in rats pretreated with high dose of metoprolol vs controls (10% vs 33%, $p = 0.044$). Mortality was also lower in rats pretreated with low dose of metoprolol (14% vs 33%) but this was not statistically significant ($p = 0.115$). Mortality was similar to control group in rats pretreated with propranolol (30% in PROP 2.5 and 25% in PROP 25), ICI (27% in ICI 5 and 32% in ICI 12), milrinone (22% in MIL 50 and 29% in MIL 250), levosimendan (30% in LEVO 10 and 26% in LEVO 50) and in rats that were treated with high dose milrinone only (31% in MIL-X). We found no significant difference in mortality when we compared low dose with a high dose of each drug.

4. Discussion

The most important finding in our study was that phosphodiesterase inhibitor milrinone, a drug that does not directly act through adrenoceptors, induced takotsubo-like cardiac dysfunction in rats. This finding challenges the concept that high levels of circulating catecholamines or excessive direct stimulation of myocardial-adrenergic receptors are necessary for the development of takotsubo syndrome.

We also showed that a high dose of levosimendan exacerbated isoprenaline-induced takotsubo-like cardiac dysfunction and that selective blockade of $beta_1$ but not $beta_2$-adrenoreceptors, reduced the extent of akinesia. Taken together, these results indicate that excessive inotropic and chronotropic stimulation; and that $beta_1$ rather than $beta_2$-adrenoreceptors play an important role in the pathophysiology of TS.

A previous study in rats suggested that $beta_2$-receptor stimulation with sequential activation of inhibitory G-proteins plays an important role in TS [13]. Our findings effectively refute this theory based on at least three different reasons. First, we induced takotsubo-like cardiac dysfunction with milrinone which does not act on adrenergic receptors. Second, milrinone increases intracellular cAMP (via inhibition of phosphodiesterase III) in contrast to inhibitory Gi protein activated by $beta_2$-receptor (which decreases cAMP). Third, the selective $beta_2$-adrenoceptor antagonist did not prevent TS.

Our finding that experimental TS could be triggered by administration of milrinone alone, a vasodilator drug that has no direct myocardial-beta adrenergic effect, implies that TS can be caused without direct adrenoreceptor stimulationn. This finding is consistent with the fact that not all patients with TS have increased catecholamines in blood. Furthermore, many patients with TS have paradoxically low level of peripheral sympathetic nerve activity. Hence, it is possible that TS can occur in the absence of direct adrenoreceptor overactivation.

The finding that heart rate and rate-pressure product, but not blood pressure, after isoprenaline administration were positively associated with the extent of akinesia challenges reductionistic concepts in which alterations in heart rate, blood pressure, and peripheral vascular resistance are not involved in the pathophysiology of TS [13]. In the present study, drugs that increase inotropy and chronotropy exacerbated whereas drugs that decrease inotropy and chronotropy attenuated isoprenaline-induced experimental TS [14–20]. Future studies are necessary to determine to which extent these drugs' effects on the severity of experimental TS relate specifically to changes in inotropy or chronotropy [21–23].

Current treatment recommendations suggest a conservative approach in patients with TS [7]. Inotropes, including milrinone, are regarded as contraindicated because these agents can aggravate patient's condition and increase mortality in TS [7,24–26]. Some authors advocate the use of levosimendan in patients with TS who develop severe heart failure. However, our experimental results indicate that levosimendan could be harmful in TS. The guidelines endorse beta-blockers and ACE-inhibitors in hemodynamically stable patients. Although several studies have shown no benefit of beta-blockers in the prevention of recurrent TS, these agents are recommended in patients with higher risk [2,5,27]. In this study, we found a dose-dependent negative relationship between beta-blockade and the extent of takotsubo-like dysfunction. Also, blockade of $beta_1$-adrenoceptors but not $beta_2$ increased survival. Therefore, our data provide an experimental rationale for the use of $beta_1$ blockade in stable patients with TS.

The strengths of this study are the high number of animals and that we have evaluated the common pharmacological agents that are used in treatment of TS. We tested these pharmacological interventions in a clinically relevant in vivo animal model that reproduces the most important characteristics of TS in humans. The major limitation is that we did not provide the precise molecular mechanism of how the different drugs influence experimental TS. However, these mechanisms are likely to be complex, and would be beyond the scope of a single manuscript. Other limitations include the lack of data on serum catecholamines, atrial natriuretic peptide and B-type natriuretic peptide; and the use of supra-physiological doses of the study drugs.

In conclusion, phosphodiesterase inhibitors induce takotsubo-like dysfunction in rats. Inhibition of $beta_1$ adrenergic receptors prevented takotsubo-like dysfunction in rats whereas inhibition of $beta_2$ adrenergic receptors did not. These findings challenge the notion that high levels of circulating catecholamines or excessive stimulation of $beta_2$ adrenergic receptors are necessary for the development of takotsubo syndrome. Our study provides an experimental foundation for avoidance of inotropes in treatment of patients with TS.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.045.

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Conflicts of interest

There are no conflicts of interest.

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