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ORIGINAL RESEARCH ARTICLE

The importance of heart rate in isoprenaline-induced takotsubo-like cardiac dysfunction in rats

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Abstract

Aims Takotsubo syndrome (TS) is an acute cardiac syndrome characterized by regional myocardial akinesia that cannot be attributed to a culprit lesion in coronary arteries. Cardiac overstimulation by catecholamines in the setting of stress is implicated in the pathogenesis of TS. While catecholamine-induced alterations in cardiac contractility have been studied as part of the causal pathway in TS, the importance of catecholamine-mediated tachycardia has not been studied. Our aim was to explore whether the reduction in heart rate, either by pharmacological suppression of the sinoatrial node with ivabradine or by surgical induction of third-degree atrioventricular block, prevents isoprenaline-induced TS-like akinesia in an experimental animal model.

Methods and results We used 142 female Sprague–Dawley rats in two separate protocols. The TS-like phenotype was induced by an intraperitoneal bolus dose of isoprenaline (ISO) 50 mg/kg. In the first protocol, we randomized 54 rats to ivabradine 10 min before ISO (IVAB1), ivabradine 10 min after ISO (IVAB2), or saline 10 min before ISO (CONTROL). In the second protocol, we randomized 88 rats to surgically induced complete heart block (CHB) or sham operation (CTRL) 10 min before the administration of ISO. All drugs were administered intraperitoneally. We recorded heart rate and blood pressure invasively in the right carotid artery. Cardiac morphology and function were evaluated by high-resolution echocardiography (VisualSonics 770 VEVO, Toronto, Ontario, Canada) 90 min after ISO injection. IVAB1 and IVAB2 rats had significantly lower heart rate and less pronounced TS-like cardiac dysfunction than CONTROL. CHB rats had a lower (54%) heart rate, and no animal developed left ventricular akinesia. In the first protocol, the CONTROL group had a median degree of akinesia of 10.2 [inter-quartile range (IQR) 0.0–18.6]. The IVAB1 group showed a median of akinesia of 0% (IQR 0.0–0.0, $P < 0.001$ vs. CONTROL). In the IVAB2 group, 5% had TS-like dysfunction ($P = 0.001$). Ejection fraction was higher in both the IVAB1 (92%, IQR 89–95) and IVAB2 groups (93%, IQR 87–96) than in the CONTROL group (78%, IQR 63–87, $P < 0.05$). In the second protocol, the median degree of akinesia in the CTRL group was 21.9% (IQR 8.9–24.6). In the CHB group, no rat developed akinesia (median 0%; IQR 0.0–0.0, $P < 0.001$ vs. CONTROL). Ejection fraction was higher in the CHB group (90%, IQR 87–92) than in the CTRL group (51%, IQR 87–92, $P < 0.05$).

Conclusions Isoprenaline-induced TS-like cardiac dysfunction can be prevented by lowering heart rate. Tachycardia may be an important part of the causal pathway in TS.

Keywords Takotsubo syndrome; Isoprenaline; Ivabradine

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Introduction

Takotsubo syndrome (TS) is an increasingly recognized acute cardiac syndrome that has a similar clinical picture to acute myocardial infarction (AMI). But unlike AMI, in TS, the myocardial akinesia does not follow a culprit coronary artery occlusion territory. The typical form of TS is characterized by akinetic apex and hyperkinetic base of the left ventricle (LV).[1] In contrast, the atypical types of TS are characterized by focal circumferential akinesia at mid-ventricle,[23] or the base of LV.[2] TS is not a benign condition, as was initially thought because it can lead to severe complications.[4] TS is reported to have similar mortality to myocardial infarction.[5] Therefore, understanding the pathogenesis of TS, which is still mostly unknown, is essential for the establishment of treatment and prevention of TS.

Patients with TS have excessive plasma catecholamines,[6,7] and endogenous and exogenous catecholamines have been shown to induce TS.[7–10] Catecholamines mediate their effects on cardiomyocytes via β-adrenergic receptors, which leads to increased heart rate and increased contractile force.[11] Catecholamines have been postulated to induce TS via β-adrenoreceptor-mediated alterations in cardiac inotropy,[12] but the role of heart rate in the pathophysiology of TS has not been explored in depth. In our rat model, which has been reproduced independently by others,[11,13,14] isoprenaline administration leads to increased contractile function and high heart rate, followed by TS-like cardiac dysfunction. In this model, TS-like cardiac dysfunction is exaggerated by cardiostimulants and attenuated by cardiodepressant, drugs that affect both cardiac inotropy and heart rate.

This study aimed to explore whether the reduction in heart rate, either by pharmacological suppression of the sinoatrial (SA) node or by surgical induction of complete heart block (CHB) at the atrioventricular (AV) node, prevents isoprenaline-induced TS phenotype in rats.

Methods

We followed National Institutes of Health guidelines for using animals in medical research. Ethics Committee at Gothenburg University approved the study protocol. We used a total number of 142 female Sprague–Dawley rats in this study. The animals were housed in a temperature-controlled facility (25°C) with 12 h light/dark cycle and were given free access to food and water.

We used a combination of ketamine (50 mg/kg) and midazolam (5 mg/kg) given intraperitoneally as anaesthesia during echocardiography, surgery, and haemodynamic monitoring in a subset of rats. For haemodynamic recordings, the rats were anaesthetized, and the hair over the neck and chest was removed with an electrical clipper and hair removal cream. The rats were then placed in a supine position on a heating pad. The settings of the heating pad were adjusted to keep the rat's temperature at 38 ± 0.2°C for 10 min under baseline conditions. Thereafter, the settings of the heating pad were kept for the rest of the experiment time. The right common carotid artery was dissected free and cannulated to record blood pressure and pulse rate continuously. Additional ketamine and midazolam were given to the rats to ensure maintenance anaesthesia for the whole period of the experiment.

Study protocol

This study is based on our rat model of isoprenaline-induced TS-like dysfunction in rats,[11] where a single dose of 50 mg/kg isoprenaline given intraperitoneally induced TS-like dysfunction in rats. Our aim was to study whether induction of bradycardia, at SA or AV node, can prevent the development of isoprenaline-induced TS-like phenotype in rats. To this end, we designed two separate protocols. In the first protocol (*Figure 1A*), 54 rats were randomized to receive ivabradine 10 mg/kg i.p. 10 min before isoprenaline (IVAB1, n = 18), ivabradine 10 mg/kg i.p. 10 min after isoprenaline (IVAB2, n = 18), or saline 10 min before isoprenaline (CONTROL, n = 18). A subset consisting of six rats from each group were used to invasively study blood pressure and heart rate (*Figure 1B*). Echocardiography was performed 90 min after isoprenaline injection to study left ventricular function and TS development.

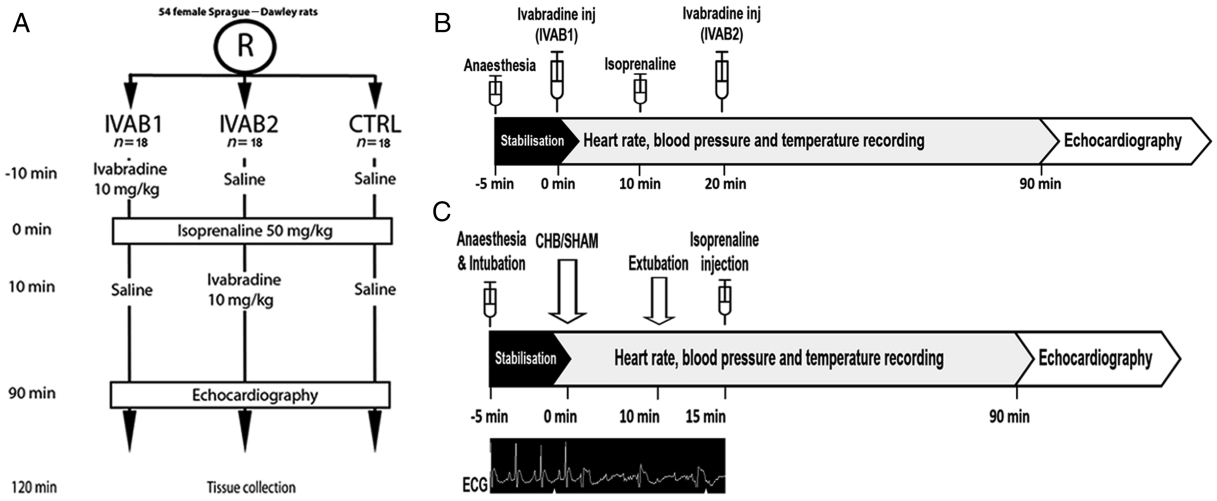
In the second protocol, 88 rats were randomized to have either sham operation as the control group (CTRL, n = 44) or the CHB group (n = 44). A subset of rats from sham (CTRL, n = 7) and CHB (n = 8) were used for invasive measurements of blood pressure and heart rate (*Figure 1C*). All rats received bolus isoprenaline 50 mg/kg i.p. 10 min after the operation. Echocardiography was performed 90 min after isoprenaline injection to evaluate LV for TS development.

The animals were euthanized immediately after the examination with echocardiography and evaluation of *in vivo* haemodynamics. The rats were unconscious under general anaesthesia with ketamine and midazolam and were continuously monitored for the duration of the whole experimental protocol. All investigators who were involved in animal care and *in vivo* experimentation had formal training in animal wellfare, animal handling, and *in vivo* experimentation according to the regulation stipulated by the Swedish law.

Surgical induction of complete heart block

After induction of anaesthesia by ketamine 50 mg/kg i.p. and midazolam 5 mg/kg i.p., the rats were intubated, placed on a heating pad in a supine position, and mechanically ventilated. Electrocardiogram (ECG) electrodes were connected from

Figure 1 Study design. (A) Study design for experiments with ivabradine. (B) Study design for experiments with ivabradine and invasive evaluation of haemodynamics. (C) Study design for experiments with complete heart block (CHB). ECG, electrocardiogram.



limbs to a digitalized system that records, displays, and analyses ECG and blood pressure (Pharmlab AstraZeneca, Möndal, Sweden). The body temperature was kept at 38 ± 0.2°C by controlling the heating pad. Following the shaving of chest hair, we made parasternal paramedian incision made on the left side, and the chest wall was opened. After stripping the thin pericardial layer, the free edge of the right atrium was carefully retracted laterally with tissue forceps to expose the groove between the right atrium and the ascending aorta. Acupuncture needle (Seirin J type 0.12 × 30 mm) was used to locate the AV node. The needle was entered at a point 1 mm parallel to the lateral aortic root through the distinctive fat pad. The fat pad is consistently found between the aortic root and the right atrium. The acupuncture needle was then advanced 2 mm in the direction of the left ventricular apex. The location of the needle tip at the AV node is verified by ECG changes in the form of rapid-onset bradycardia and AV block. Unipolar diathermy was then attached to the free end of the needle to disrupt AV node. AV node was thus cauterized under ECG control to establish a CHB. Haemostasis was ensured, the chest wall was closed, and the animals were extubated and kept under maintenance of anaesthesia and analgesia. The animals with persistent CHB lasting for 15 min were included in the study.

Invasive evaluation of haemodynamics

Blood pressure and heart rate were evaluated invasively while the rats were anaesthetized with ketamine and midazolam. We dissected free and cannulated the right common carotid artery. We then connected the cannula through a pressure sensor (Pharmlab Astra Zeneca, Mölndal, Sweden). We recorded blood pressure and pulse rate continuously over a period of 90 min. We evaluated the adequacy of the anaesthesia by gentle paw pinching. If the rat reacted to the stimulus, we provided additional boluses of ketamine and midazolam. Immediately after invasive haemodynamic recordings, the rats underwent an echocardiographic evaluation, after which they were euthanized. We calculated dP/dt_{max} and dP/dt_{min} derived from the arterial systolic and diastolic pressure curves.[15]

Echocardiography

To study cardiac function and quantify left ventricular akinesia 90 min after isoprenaline administration, we used VisualSonics 770 VEVO imaging station, which has an integrated rail system for consistent positioning of the ultrasound probe. For imaging, we used a 35 MHz linear transducer (RMV 707). An optimal parasternal long-axis view (i.e. visualization of both the mitral and aortic valves and maximum distance between the aortic valve and the cardiac apex) was achieved. A cine loop of $>$1000 frames was acquired using the ECG-gated kilohertz visualization technique. The extent of akinesia was traced in the long axis along the endocardial border and expressed as a percentage of total left ventricular endocardial length. Fractional area change, an index of cardiac function, was calculated as FS = (EDA − ESA) EDA, where EDA and ESA are end-diastolic and end-systolic areas, respectively. We defined the presence of TS when the extent of akinesia was $\geq$20%. One operator with a long experience of echocardiography in small animals performed all examinations. We have good agreement for the intraobserver and interobserver coefficients of variation (5.1 and 7.3, respectively) for assessment of segmental contractility at our laboratory.[16]

Statistics

We used the Shapiro–Wilk test and histograms to evaluate whether data were normally distributed. Kruskal–Wallis or Mann–Whitney *U* test was used for comparison of akinesia between groups. For comparison of blood pressure and heart rate over time between groups, we modelled the data with linear mixed regression. χ^2 test for trend was used for mortality comparison. Data were expressed as mean ± standard deviation. All reported *P* values are two sided and are not adjusted for multiple testing. Stata software (Version 16.1, StataCorp, College Station, Texas, USA) was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Left ventricular apical akinesia

In the first protocol with ivabradine, the CONTROL group had a median degree of akinesia of 10.2 [inter-quartile range (IQR) 0.00–18.59]. TS-like dysfunction was detected in 50% of rats in this group. The IVAB1 group showed a median of akinesia of 0% (IQR 0.00–0.00, $P < 0.001$ vs. CONTROL), while the incidence of akinesia was 0% ($P < 0.001$ vs. CONTROL). The IVAB2 group has a median of akinesia of 0% (IQR 0.00–0.00, $P < 0.001$ vs. CONTROL). Five per cent of animals in the IVAB2 group showed TS-like dysfunction ($P = 0.001$ vs. CONTROL) (*Figures 2* and *3A* and Supporting Information,

Figure 2 Long-axis echocardiographic view of the left ventricle (LV) in end-systole. (A) Development of takotsubo syndrome phenotype induced by isoprenaline. Arrows indicated presence of akinesia in the apical segments—'apical ballooning'. (B) Complete heart block abolished development of isoprenaline-induced apical ballooning. No rat developed apical ballooning. (C) Ivabradine attenuated development of isoprenaline-induced apical ballooning. A, apex; Ao, aorta; AW, anterior wall; B, base; BW, posterior wall; ECG, electrocardiogram; HR, heart rate; LA, left atrium.

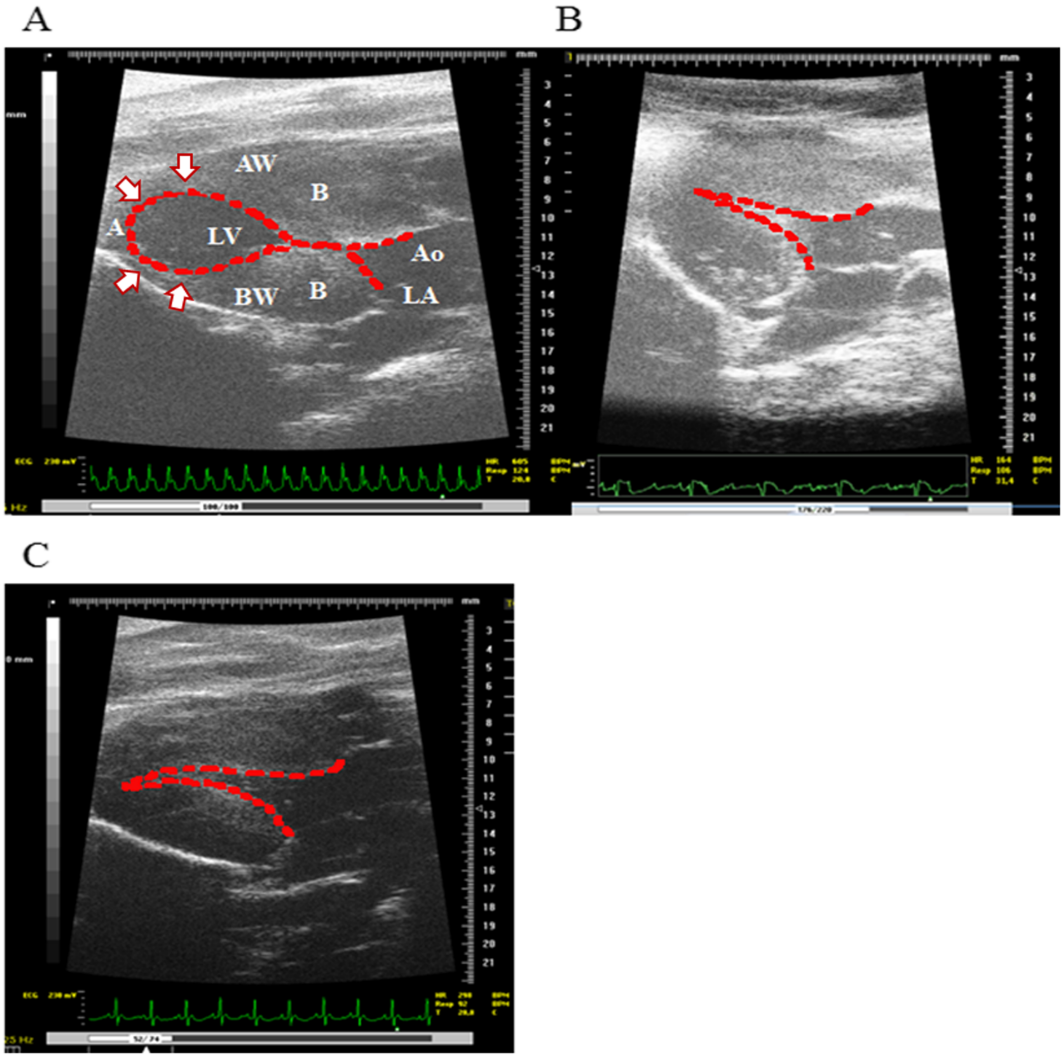


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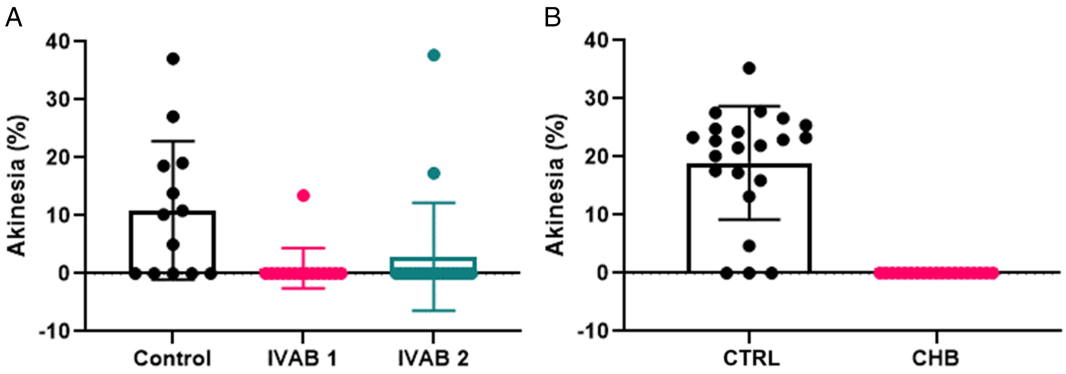
Figure 3 Median degree of akinesia in the left ventricle. (A) Effects of ivabradine (IVAB1 and IVAB2) on isoprenaline-induced akinesia in the left ventricle. (B) Effects of complete heart block (CHB) on isoprenaline-induced akinesia in the left ventricle.



Video S1). In the second protocol with CHB, the median degree of akinesia in the CONTROL group was 21.9% (IQR 8.92–24.56), while TS-like cardiac dysfunction was observed in 50% of these rats. In contrast, in the CHB group, no rat developed akinesia (median 0%; IQR 0.00–0.00, $P < 0.001$ vs. CONTROL) (*Figures 2* and *3B* and Supporting Information, *Video S1*).

Heart rate and blood pressure

Isoprenaline administration significantly increased heart rate during the first 60 min (CONTROL). Ivabradine reduced heart rate significantly, irrespective of whether it was given before isoprenaline (IVAB1 group) or after isoprenaline (IVAB2 group) (*Figure 4A*). In contrast, neither systolic nor diastolic blood pressure was significantly different between IVAB1, IVAB2, and CTRL (*Figure 5A*). In comparison with the CTRL group, both heart rate (*Figure 4B*) and systolic blood pressure (*Figure 5B*) were lower in the CHB group for the entire period of the experiment. At 60 min after isoprenaline administration, the heart rate was 175 ± 15 b.p.m. in the CHB group and 590 ± 10 b.p.m. in the CTRL group ($P < 0.001$). For the duration of the experimental time (60 min), dP/dt_{max} and dP/dt_{min} derived from arterial blood pressure were significantly higher in the IVAB2 group than in the CONTROL group ($P < 0.0001$). No difference was found between the IVAB1 group and the CONTROL group ($P = 0.523$) (*Table 1*). We found no difference in dP/dt_{max} and dP/dt_{min} between the CTRL group and the CHB group ($P = 0.165$) (*Table 2*).

Echocardiography

In the first protocol with ivabradine, the CONTROL group had lower ejection fraction (78%; IQR 63–87, $P < 0.05$) than the IVAB1 (92%; IQR 89–95, $P < 0.05$) and IVAB2 groups (93%; IQR 87–96, $P < 0.05$) (*Table 3*). In the second protocol with CHB, ejection fraction was lower (51%; IQR 44–58) in the CONTROL group than in the CHB group (90%; IQR 87–92, $P < 0.05$) (*Table 4*).

Mortality

In the first protocol, mortality was 29% in the CONTROL group, 35% in the IVAB1 group ($P = 0.64$ vs. CONTROL), and 20% in the IVAB2 group ($P = 0.50$ vs. CONTROL). In the second protocol, the mortality was 28% in the CTRL group and 37% in the CHB group ($P = 0.37$).

Discussion

The main finding in this study is that a reduction in heart rate, either pharmacologically by the SA-node inhibitor ivabradine or mechanically by the surgical induction of CHB, prevents isoprenaline-induced TS-like dysfunction in the rat. This finding implies that the heart rate plays a causative role in the pathogenesis of TS.

This paper builds on our previous work in which we have shown that isoprenaline administration to rats induces tachycardia, hypotension, and typical apical TS-like dysfunction. In contrast, epinephrine and norepinephrine induce hypertension, a much less pronounced elevation of heart rate and atypical basal TS-like dysfunction.[11,17,18] In our previous work,[11,17] co-administration of the hypotensive drug hydralazine with epinephrine or norepinephrine lowered blood pressure and increased heart rate and lead to the development of the typical apical TS-like dysfunction observed with isoprenaline. Perhaps more importantly, co-administration of phenylephrine with isoprenaline resulted in higher blood pressure and lower heart rate and prevented TS-like cardiac

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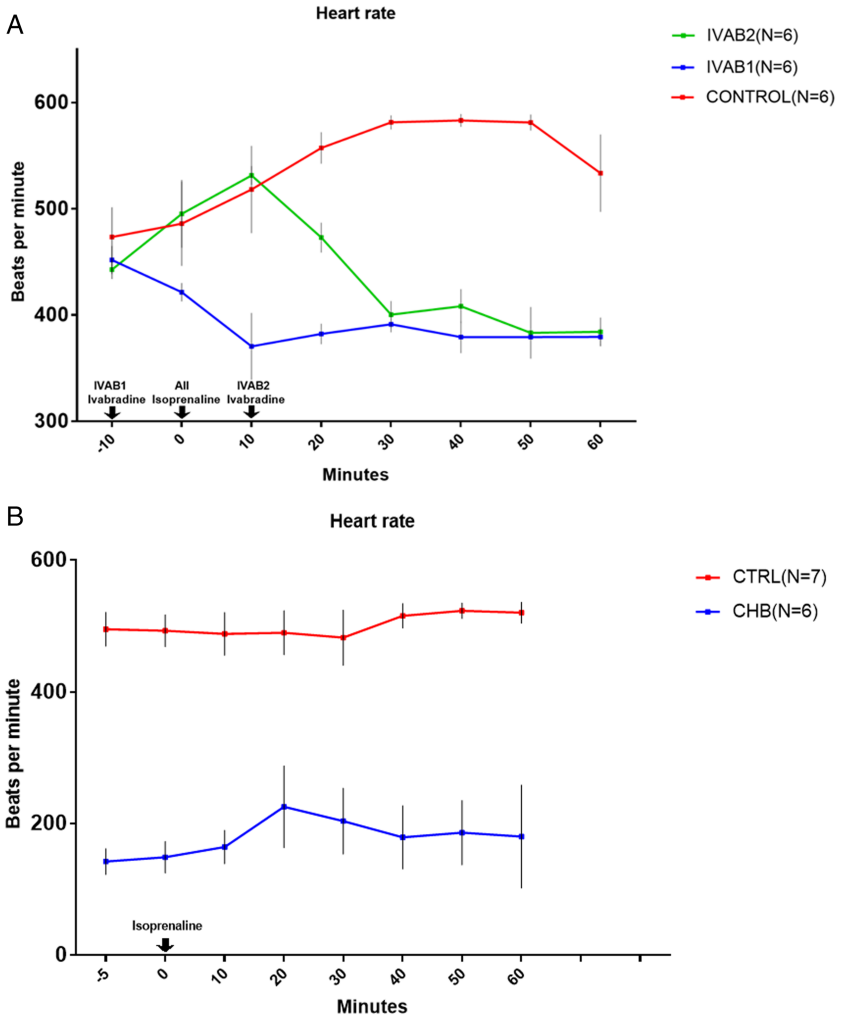
Figure 4 Heart rate. (A) Effect of ivabradine on isoprenaline-induced changes in heart rate. (B) Effect of surgical complete heart block (CHB) on isoprenaline-induced changes in heart rate. CONTROL, control group for the ivabradine experiment; CTRL, control group for the CHB experiment; IVAB1, ivabradine administered 10 min prior to isoprenaline; IVAB2, ivabradine administered 10 min after isoprenaline.



dysfunction. An increase in heart rate has been reported before the development of the TS-like phenotype in the non-human primate model.[19]

The present study confirms this association between heart rate and experimental TS-like cardiac dysfunction by testing the simple yet important hypothesis that heart rate is causally involved in the development of isoprenaline-induced TS-like cardiac dysfunction. By reducing the heart rate, either pharmacologically using the SA-node inhibitor ivabradine or mechanically by the surgical induction of CHB, we could completely prevent the development of apical akinesia—a hallmark of the TS. The experimental design is simple and straightforward, yet the study provides clear-cut evidence that heart rate is indeed causally involved in the development of takotsubo-like cardiac dysfunction. Our aim was not to address the intricate cellular and molecular mechanisms behind these results, but rather to avoid oversimplification of complex biological phenomena, which has characterized several previous experimental studies of the TS.[11,13,20] Rather than being provided in its entirety from a single experimental study, knowledge about mechanisms of the TS will likely come gradually from several properly designed and carefully executed experimental and clinical studies. Future studies are needed to build on our findings and further examine the association between acute alterations in heart rate, afterload, and TS-like cardiac dysfunction.

Irrespective of the exact underlying mechanisms, an important role of heart rate in the pathogenesis of TS is consistent with several of the leading hypotheses regarding the pathophysiology behind TS. At higher heart rates, the heart spends relatively more time in systole than at lower heart rates. Tachycardia reduces coronary perfusion and increases cardiac metabolic demand. Tachycardia could, therefore, contribute to the occurrence of metabolic supply–demand

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Figure 5 Systolic blood pressure. (A) Effect of ivabradine on isoprenaline-induced changes in systolic blood pressure. (B) Effect of surgical complete heart block (CHB) on isoprenaline-induced changes in systolic blood pressure. CONTROL, control group for the ivabradine experiment; CTRL, control group for the CHB experiment; IVAB1, ivabradine administered 10 min prior to isoprenaline; IVAB2, ivabradine administered 10 min after isoprenaline.

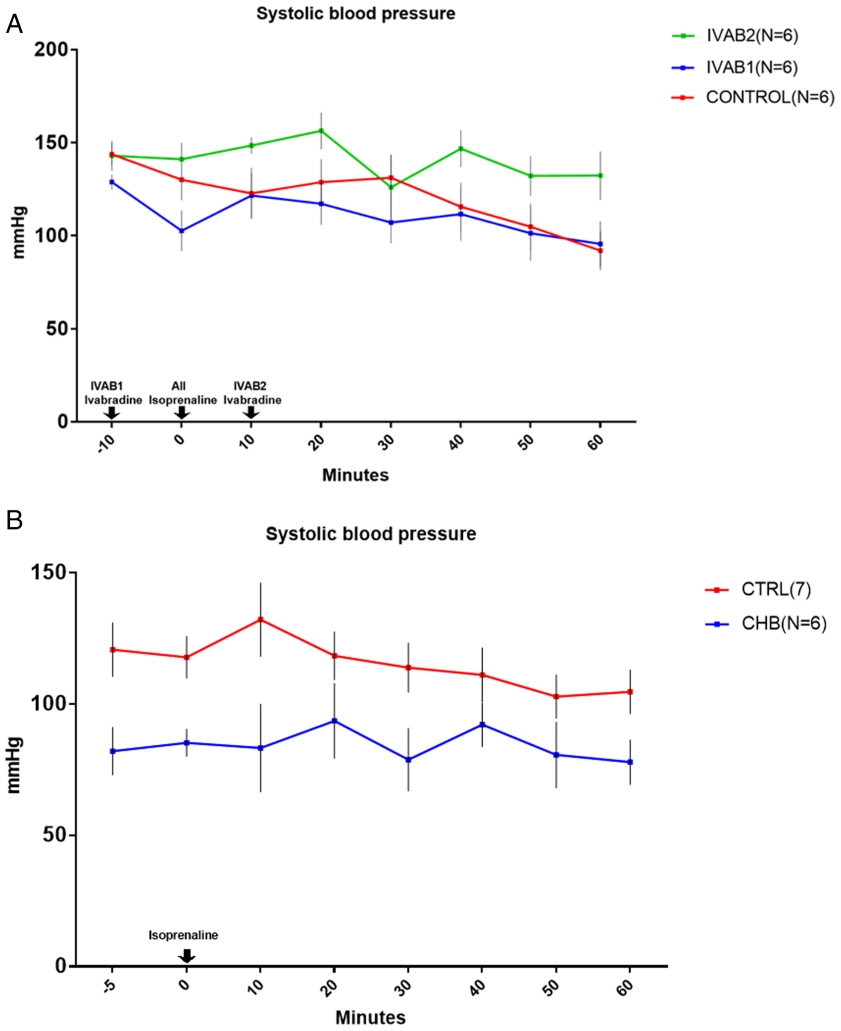

Table 1 dP/dt_{max} and dP/dt_{min} derived from the arterial systolic and diastolic pressure

Time (min)	CONTROL (n = 6)		IVAB1 (n = 6)		IVAB2 (n = 6)	
	Mean (±SD)		Mean (±SD)		Mean (±SD)	
	dP/dt_{max}	dP/dt_{min}	dP/dt_{max}	dP/dt_{min}	dP/dt_{max}	dP/dt_{min}
−5	1844.9 (1440.0)	−640.5 (510.4)	2065.1 (1404.5)	−647.9 (557.8)	4447.9 (2661.0)	−1838.6 (1405.7)
0	2877.5 (1940.6)	−955.3 (536.4)	2709.9 (1302.9)	−721.9 (371.9)	2780.7 (1593.2)	−1029.7 (534.4)
10	3995.2 (2346.7)	−1718.5 (1260.3)	2694.6 (1181.1)	−832.1 (382.9)	3094.4 (980.3)	−1269.8 (404.9)
20	3112.5 (1954.4)	−1463.2 (1048.6)	2468.6 (1423.4)	−758.4 (543.4)	3176.0 (753.6)	−1344.9 (465.9)
30	3695.9 (2493.0)	−1934.7 (1534.1)	2596.0 (1065.1)	−760.5 (338.7)	2802.4 (1424.7)	−1084.2 (549.9)
40	3314.9 (2665.1)	−1726.3 (1588.2)	2514.7 (1101.4)	−754.2 (405.3)	3086.9 (1968.8)	−1283.1 (803.5)
50	4392.3 (3486.1)	−2316.9 (2137.8)	2866.2 (1439.9)	−995.9 (680.9)	4177.3 (2595.3)	−1971.3 (1324.3)
60	4714.2 (3135.5)	−2138.4 (1542.4)	2774.1 (1310.3)	−863.8 (418.6)	4946.7 (2958.3)	−2225.6 (1345.6)

CONTROL, control; IVAB, ivabradine; SD, standard deviation.
Values represent mean and SD. In the linear mixed model with group as a fixed effect variable and time as a random effect variable, dP/dt_{max} and dP/dt_{min} were significantly higher in the IVAB2 group than in the CONTROL group ($P < 0.0001$). No difference was found between the IVAB1 group and the CONTROL group ($P = 0.523$).

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Table 2 dP/dt_{max} and dP/dt_{min} derived from the arterial systolic and diastolic pressure

Time (min)	CTRL (n = 6) Mean (±SD)		CHB (n = 6) Mean (±SD)	
	dP/dt_{max}	dP/dt_{min}	dP/dt_{max}	dP/dt_{min}
−5	4409.2 (1672.7)	−1929.3 (555.8)	3654.1 (1852.9)	−1251.6 (625.3)
0	4241.2 (2989.6)	−1258.6 (676.4)	3936.6 (2869.5)	−1173.3 (980.4)
10	4126.6 (2358.3)	−1224.5 (617.9)	3888.7 (1300.8)	−1404.1 (481.4)
20	4902.0 (1441.0)	−1542.7 (352.3)	4113.3 (841.4)	−1708.8 (398.2)
30	5464.1 (1280.0)	−1674.5 (358.6)	3473.3 (1639.6)	−1351.6 (539.1)
40	5432.9 (1844.4)	−1764.3 (724.0)	4304.1 (2382.9)	−1420.4 (569.9)
50	5532.5 (1655.8)	−1881.3 (650.6)	4575.7 (2089.7)	−1676.9 (537.1)
60	5523.1 (1393.3)	−1854.1 (643.1)	3319.4 (1465.6)	−1324.9 (563.7)

CHB, complete heart block; CTRL, control; SD, standard deviation.
Values represent mean and SD. In the linear mixed model with group as a fixed effect variable and time as a random effect variable, there was no difference in dP/dt_{max} and dP/dt_{min} between the CTRL group and the CHB group (P = 0.165).

Table 3 Echocardiographic evaluation of cardiac function and morphology (Protocol 1, ivabradine)

	CONTROL	IVAB1	IVAB2
Akinesia (%)	10.2 (4.7)	0 (0.0)	0 (0.0)
End-diastolic area (mm^2)	61 (3.5)	62 (3.8)	64 (4.3)
End-systolic area (mm^2)	26 (5.8)	14 (2.5)*	13 (3.0)*
Fractional area change (%)	58 (5.7)	75 (3.0)*	78 (3.5)*
LV volume in diastole (mm^2)	241 (27.5)	259 (27.5)	281 (32.5)
LV volume in systole (mm^2)	52 (23.7)	17 (8.5)*	16 (8.0)*
Stroke volume (μL)	190 (15.8)	237 (29.0)	238 (33.5)
Cardiac output (mL/min)	101 (1.7)	91 (1.2)*	91 (3.6)*
Ejection fraction (%)	78 (6.0)	92 (1.5)*	93 (2.2)*

CONTROL, control; LV, left ventricular.
Values represent mean and standard deviation.
*P < 0.05 vs. CONTROL.

Table 4 Echocardiographic evaluation of cardiac function and morphology (Protocol 2, CHB)

	CTRL	CHB
Akinesia (%)	22.4 (8.9)	0 (0.0)*
End-diastolic area (mm^2)	46 (2.7)	59 (8.0)*
End-systolic area (mm^2)	30 (2.7)	16 (2.0)*
Fractional area change (%)	33 (3.5)	73 (1.7)*
LV volume in diastole (mm^2)	166 (18.5)	274 (66.2)*
LV volume in systole (mm^2)	78 (16.7)	27 (4.2)*
Stroke volume (μL)	87 (17.8)	247 (62.7)*
Cardiac output (mL/min)	44 (2.5)	45 (0.7)
Ejection fraction (%)	51 (3.5)	90 (1.3)*

CHB, complete heart block; CTRL, control; LV, left ventricular.
Values represent mean and standard deviation.
*P < 0.05 vs. CTRL.

mismatch in the heart, which has been suggested to be involved in the pathogenesis of TS.[8,20] A role for myocardial supply–demand mismatch in the pathogenesis of TS is consistent with most of the current hypotheses regarding TS pathophysiology.[8,20,21] A supply–demand mismatch would be expected to occur on the basis of excess demand in the presence of excess left ventricular afterload (e.g. dynamic outflow tract obstruction) and on the basis of reduced supply in the presence of perfusion defects (coronary artery spasm,[1,22] spontaneously dissolved thrombus,[23] or coronary microvascular dysfunction[22]). In all these scenarios, the cardiac metabolic supply–demand mismatch could be exacerbated by a high heart rate. Because tachycardia can contribute to supply–demand mismatch, and because high heart rate has been linked to increased risk of malignant ventricular arrhythmias,[24] the observed association between tachycardia and TS is also compatible with the hypothesis that TS is a form protective stunning, through which the heart ceases contractile work to preserve energy for maintenance of vital cellular processes and electrophysiological stability in situations of cardiomyocyte stress.[25]

Another hypothesis is that direct catecholamine effects or toxicity on the cardiomyocytes induces contractile dysfunction.[21] The link between a high heart rate and direct catecholamine effects in the pathophysiology of TS is less straightforward. In theory, a high heart rate could influence the depolarization and repolarization patterns across the myocardium, which could affect the activity and distribution of β-adrenergic receptors across different regions within the heart.[21] This hypothesis should be addressed in future studies. Irrespective of the exact underlying mechanisms, our study provides compelling evidence that a high heart rate is important for the development of isoprenaline-induced experimental TS in rats.

An important strength of this study is that it is based on a well-established and reproducible rat model of isoprenaline-induced apical TS. However, the model is experimental and is based on the administration of a high dose of a synthetic catecholamine. Although we provide compelling evidence for the importance of heart rate in isoprenaline-induced experimental TS by using two different experimental set-ups (pharmacological reduction by targeting the SA node and surgical reduction by ablating the AV node), we did not address the detailed mechanisms through which a high heart rate contributes to TS-like dysfunction.

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Conclusions

Isoprenaline-induced experimental TS-like cardiac dysfunction can be prevented by mitigating the isoprenaline-induced increase in heart rate.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information

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