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Different catecholamines induce different patterns of takotsubo-like cardiac dysfunction in an apparently afterload dependent manner

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ABSTRACT

Background: Takotsubo cardiomyopathy (TCM) is characterized by regional left ventricular dysfunction that cannot be explained by an occlusive lesion in a coronary artery. Catecholamines are implicated in the pathogenesis of TCM but the mechanisms involved are unknown. Because the endogenous and the most commonly used exogenous catecholamines have well defined adrenoceptor subtype affinities, inferences can be made about the importance of each adrenoceptor subtype based on the ability of different catecholamines to induce TCM. We therefore studied which of five well-known catecholamines, that differ in receptor subtype affinity, are able to induce TCM-like cardiac dysfunction in the rat.

Methods: 255 rats received intraperitoneally isoprenaline (β_1/β_2-adrenoceptor agonist), epinephrine ($\beta_1/\beta_2/\alpha$-adrenoceptor agonist), norepinephrine (β_1/α-adrenoceptor agonist), dopamine ($\alpha/\beta_1/\beta_2$-adrenoceptor agonist) or phenylephrine (α-adrenoceptor agonist). Each catecholamine was given in five different doses. We measured blood pressure through a catheter inserted in the right carotid artery and studied cardiac morphology and function by echocardiography.

Results: All catecholamines induced takotsubo-like cardiac dysfunction. Isoprenaline induced low blood pressure and predominantly apical dysfunction whereas the other catecholamines induced high blood pressure and basal dysfunction. In another set of experiments, we continuously infused hydralazine or nitroprusside to rats that received epinephrine or norepinephrine to maintain systolic blood pressure <120 mm Hg. These rats developed akinesia of the apex instead of the base. Infusion of phenylephrine to maintain blood pressure >120 mm Hg after isoprenaline administration prevented apical TCM-like dysfunction.

Conclusions: Catecholamine-induced takotsubo-like cardiac dysfunction appears to be afterload dependent rather than depend on stimulation of a specific adrenergic receptor subtype.

1. Introduction

Takotsubo cardiomyopathy (TCM) is an increasingly recognized syndrome characterized by regional left ventricular (LV) dysfunction that cannot be explained by an occlusive culprit lesion in a coronary artery. The predominant presentation is widespread akinesia in the apical segments and hyperkinesia in the basal segments, so-called "apical ballooning". However, other patterns of cardiac dysfunction exist and are being reported with increasing frequency [1]. Cardiac dysfunction is often extensive in TCM and may lead to lethal complications, including malignant arrhythmias, cardiogenic shock and ventricular rupture. However, the organ dysfunction is usually reversible. Clinical observations indicate an important role of excessive plasma catecholamine in TCM [2,3], but the precise pathophysiology behind TCM and the mechanisms underlying the remarkable recovery are unknown.

We currently lack guidelines regarding diagnosis, treatment and follow-up of TCM patients. Instead, these patients are often treated as though they suffered from an acute coronary event and heart failure, a strategy that may be counterproductive [3]. It is important to develop animal models that can aid in elucidating the mechanisms behind this syndrome and serve as a platform from which to develop evidence-based treatment guidelines. Rat models have proven to be good experimental models of human heart disease and have played important roles in the development and confirmation of some of the most central concepts in cardiovascular medicine [4–6].

We and others have shown that TCM-like LV apical ballooning can be induced in rats by subjecting them to severe immobilization stress

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Table 1
Receptor specificity of the different catecholamines.

Catecholamine	β_1	β_2	α
Isoprenaline	+	+	-
Epinephrine	+	+	+
Norepinephrine	+	-	+
Dopamine[a]	+	+	+
Phenylephrine	–	-	+

+, agonist at receptor; –, no significant activity at receptor.
[a] Dopamine acts also on dopaminergic receptors (D1, D2, … D5).

or by exogenous administration of catecholamine [7,8]. However, it remains to be established through which mechanisms catecholamine induce TCM-like cardiac dysfunction. Although catecholamine-induced vasospasm has been reported and perfusion defects have been postulated to play a role in TCM, we have recently shown that coronary artery perfusion defects appear not to precede development of isoprenaline-induced TCM in rats [9].

A next step in elucidating the mechanisms behind TCM would be to decipher which of the adrenoreceptor subtypes that are responsible for causing the disease. Because the respective receptor subtype affinity profiles for the endogenous and most commonly used exogenous catecholamines have been well defined (Table 1), inferences can be made about the relative importance of each adrenoreceptor subtype in experimental TCM based on the respective ability of the different catecholamines to induce TCM [10]. We therefore set out to study which adrenergic agents are able to induce TCM-like cardiac dysfunction in the rat.

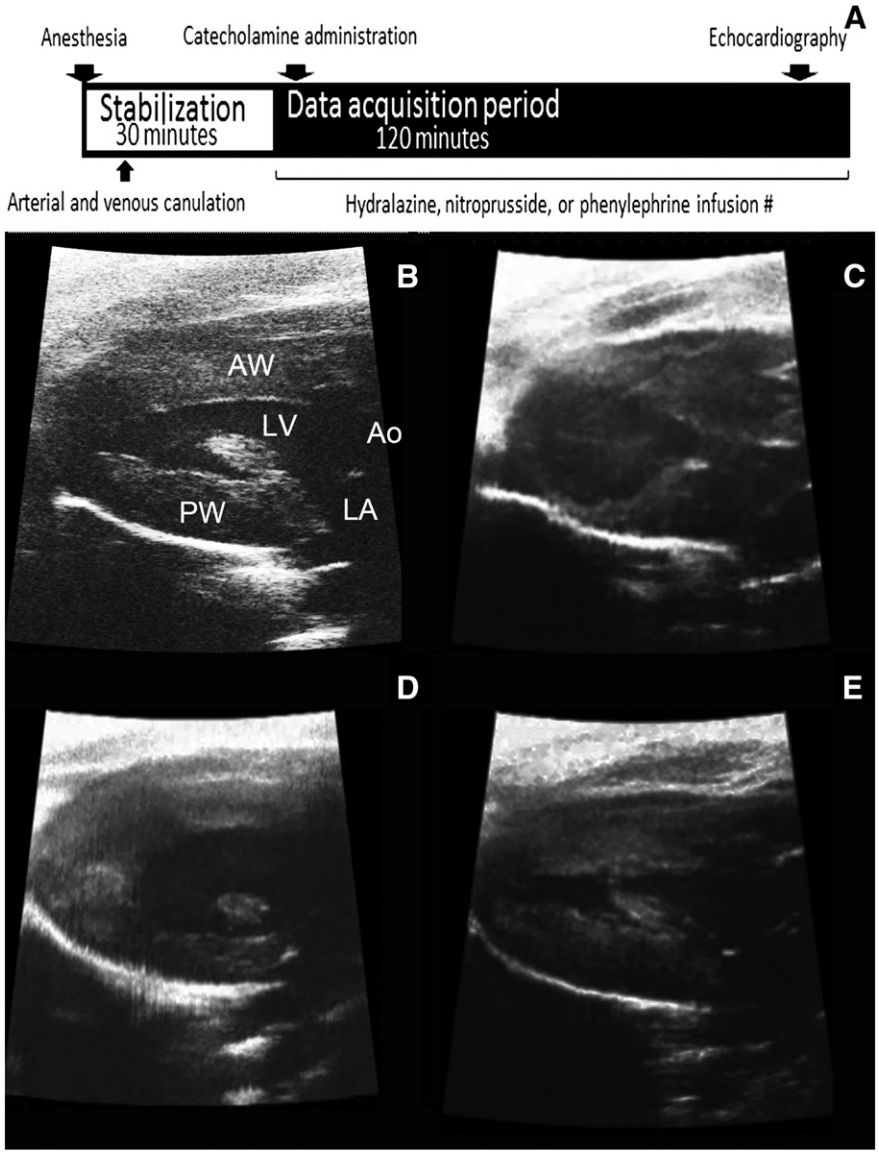

Fig. 1. Experimental setup and patterns of catecholamine-induced takotsubo-like cardiac dysfunction. *A. Experimental setup.* The rats were anesthetized on ketamine (50 mg/kg) and midazolam (5 mg/kg) and were kept anesthetized throughout the experiment. They were subsequently placed on a heated surface set to maintain body temperature at 38 ± 0.1 at baseline. Toe pinching was performed every 5 min to ensure adequate anesthesia. Once the rats had been confirmed to be unresponsive to toe-pinching, the right carotid artery and jugular vein were dissected free and canulated. A pressure-sensing catheter was inserted into the carotid artery. Once body temperature had remained stable at 38 ± 0.1 for >10 min the rats were injected with catecholamine intraperitoneally. In a subset of rats, infusions with hydralazine, nitroprusside or isoprenaline were started 1 min before catecholamine administration. Blood pressure was continuously recorded. 90 min post catecholamine administration echocardiographic assessment of degree of cardiac akinesia and cardiac function was performed. Two hours post catecholamine the rats were sacrificed. A subset of rats was allowed to recover from anesthesia and was returned to their cage. Repeat echocardiography was performed in these rats after seven days. *B–E. End-systolic images of takotsubo-like cardiac dysfunction in rats.* Parasternal long axis view. Under normal conditions, the entire LV deforms uniformly (B). Catecholamine-administration in rats may induce takotsubo-like apical (C) or basal (D) dysfunction. Cardiac function was normalized seven days post catecholamine administration (E). Ao, aorta; AW, anterior wall; DOP, dopamine; EPI, epinephrine; ISO, isoprenaline; i.p., intra-peritoneal; i.v., intravenous; LA, left atrium; LV, left ventricle; NOR, norepinephrine; PHE, phenylephrine; PW, posterior wall. # Infusions were delivered only to a subset of the rats used.