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

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**Background:** Stress induced cardiomyopathy (SIC) is an acute cardiac syndrome with symptoms reminiscent of an acute coronary syndrome but with different pathology and prognosis. As in the case of myocardial infarction part of the ventricle stops contracting and becomes akinetic, but unlike MI the akinetic part does not undergo necrosis and over time normal function is regained if the patient survives. The akinetic area does not confirm to the area of ventricle wall supplied by any one coronary artery and when angiography is performed no occlusions are found in the coronary arteries. The precise mechanism behind this is unknown, but high concentrations of catecholamines are known to play a central role. The condition is often brought on by somatic and or emotional stress. As of now there exists no evidence based treatment guidelines.

**Aims:** To study the role of the different adrenergic receptors in the development of SIC using a rat model and catecholamines with different receptor affinities. And to study how intervening to alter afterload affects size and location of the SIC-like dysfunction.

**Methods:** Ten week old male Sprague-Dawley rats weighting 250-350 g where used for all experiments. Rats where anesthetized using a mixture of ketamine and Midazolam. Catecholamines where administered as a bolus intraperitoneally. The catecholamines used where adrenaline, noradrenaline, phenylephrine, dopamine and isoprenaline all of whom display different, well established, affinities for the various adrenergic receptors. Additional drugs where administered as a continuous infusion into the right jugular vein. Left ventricular
function was studied by echocardiography and both evaluated for akinesia/no akinesia, percentage affected and fractional area change was calculated.

First maximum tolerated dose for each catecholamine was titrated, using 6 rats for each dose and 5e doses per catecholamine. Then we took the dose most likely to produce SIC-like dysfunction for each catecholamine and gave it to 7 rats while monitoring hemodynamics invasively. Then we gave adrenaline, noradrenaline and isoprenaline at the same dose while giving Hydralazine or nitroprusside to lower blood pressure in the adrenaline and noradrenaline rats and phenylephrine to increase blood pressure in the isoprenaline rats in order to alter afterload.

**Results:** All included catecholamines caused tachycardia, hair erection and increase in body temperature. All catecholamines were able to cause SIC like dysfunction in the rat heart. The catecolamines with affinity for the $\alpha$-adrenergic receptor were most likely to cause akinesia in the basal part of the ventricle whereas isoprenaline which only stimulates the $\beta$-receptors caused primarily apical akinesia. The catecholamines stimulating $\alpha$-receptors also caused hypertension in the rats while isoprenaline which only stimulates $\beta$-receptors caused hypotension.

When intervention was performed to lower blood pressure in rats receiving adrenaline or noradrenaline with Hydralazine or nitroprusside all basal akinesia disappeared and only apical akinesia was seen. When the opposite intervention was performed in hypotonic isoprenaline rats all akensia disappeared.

**Conclusion:** The ability of both $\alpha$ and $\beta$-agonists to cause SIC-like dysfunction makes it unlikely that any one adrenergic receptor is the culprit in SIC. The importance of afterload as determined by vascular tonus for the morphology of the akinesia in the heart points to a cardiovascular pathogenesis rather than simply a cardiac one.
**Ethics:** We received permission in advance for all experiments from the ethical committee for animal experiments at Sahlgrenska academy.

**Key words:** Takotsubo, Stress induced Cardiomyopathy, SIC, Tako-tsubo, heart failure, rat model