

Pathophysiology and treatment in experimental stress-induced cardiomyopathy

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg
Tisdagen den 23 september 2014 kl.13.00

Av **Björn Redfors**

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Avhandlingen baseras på följande arbeten:

I: Shao Y, Redfors B, Scharin Täng M, Möllmann H, Troidl C, Szardien S, Hamm C, Nef H, Borén J, Omerovic E.

Novel rat model reveals important roles of β -adrenoreceptors in stress-induced cardiomyopathy.
Int J Cardiol. 2013 Oct 3;168(3):1943-50.

II: Redfors B, Shao Y, Wikström J, Lyon AR, Oldfors A, Gan L, Omerovic E.

Contrast echocardiography reveals apparently normal coronary perfusion in a rat model of stress-induced (takotsubo) cardiomyopathy.

Eur Heart J Cardiovasc Imaging. 2014 Feb 15(2):152-7.

III: Redfors B, Ali A, Shao Y, Lundgren J, Gan L, Omerovic E.

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

Int J Cardiol. 2014. Jun 15;174(2):330-6.

IV: Redfors B, Shao Y, Ali A, Sun B, Omerovic E.

Rat models reveal differences in cardiocirculatory profile between takotsubo syndrome and acute myocardial infarction.

J Cardiovasc Med. 2014. Aug 8. [Epub ahead of print]

V: Redfors B, Oras J, Shao Y, Seeman-Lodding H, Ricksten SE, Omerovic E.

Cardioprotective effects of isoflurane in a rat model of stress-induced cardiomyopathy (takotsubo)

Int J Cardiol. In print.



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ABSTRACT

Background: Stress-induced cardiomyopathy (SIC) is an acute cardiac affliction associated with significant morbidity and mortality. It is characterized by potentially reversible regional myocardial akinesia which may involve up to 70% of the heart. An episode of SIC is often preceded by a strong emotional or somatic stressor. Catecholamine is implicated in the pathogenesis of SIC but the mechanisms involved are unknown. Neither American nor European guidelines provide any treatment recommendations for SIC, and no randomized clinical studies on treatment in SIC have been performed.

Aims: The aim of my thesis was to develop a representative animal model of SIC that can be used to study the pathophysiology behind the syndrome and to test potential treatment strategies.

Methods: We used 10-week-old male Sprague Dawley rats. The SIC models presented in the thesis are based on intraperitoneal administration of a catecholamine, given as a bolus. We infused fluid and/or pharmacological agents through the right jugular vein and measured arterial blood pressure through a catheter inserted in the right common carotid artery. We used small animal echocardiography to study cardiac morphology and function and performed histological analyses of cardiac tissue to detect perturbations in lipid metabolism.

Results: In manuscript I we reproduced the clinical phenomena associated with SIC in rats by administration of catecholamine.

In manuscript II we show that perfusion defects did not appear to precede the development of SIC in our rat model.

In manuscript III we show that the development and morphological type of SIC appear to depend on hemodynamic factors rather than specific adrenoceptor subtypes.

In manuscript IV we show that left ventricular filling pressure and cardiac output appear to be near-normal in experimental and clinical SIC despite hypotension. We also show that interventions for pharmacologically increased blood pressure increase acute mortality in the rat model.

In manuscript V we show, in two different experimental set-ups, that isoflurane anesthesia dose-dependently prevents experimental SIC.

Conclusion: Clinical SIC phenomena can be reliably reproduced in rat models. Because development of SIC appears to depend on hemodynamic factors, SIC should be considered a cardiocirculatory syndrome, in which the cardiomyopathy is one component. Isoflurane could be the anesthetic of choice in patients at increased risk of developing SIC, e.g. patients with severe somatic illness.

Key words: adrenoceptor, cardiocirculatory syndrome, catecholamine, echocardiography, isoflurane, stress-induced cardiomyopathy, Takotsubo cardiomyopathy,