

## Pathophysiology and treatment of Takotsubo Syndrome

### Insights from preclinical studies

#### Akademisk avhandling

Som för avläggande av medicin doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg den 2020-09-28, klockan 13:00

av **Anwar Gasim Elsieid**

Fakultetsopponent:

**Mark Petrie**, Professor/Honorary Consultant

Institute of Cardiovascular & Medical Sciences University of Glasgow, Glasgow, Storbritannien

#### Avhandlingen baseras på följande delarbeten

- I. Redfors B, Ali A, Shao Y, Lundgren J, Omerovic E. **Different catecholamines induce different patterns of Takotsubo-like cardiac dysfunction in an apparently afterload dependent manner.** Int J Cardiol. 174 (2014) 330-336
- II. Anwar Ali, Björn Redfors, Joel Lundgren, Jessica Alkhoury, Jonatan Oras, Li-Ming Gan, Omerovic E. **Effects of pretreatment with cardiostimulants and beta-blockers on isoprenaline-induced Takotsubo-like cardiac dysfunction in rats.** Int J Cardiol. 2019 Apr 15; 281:99-104
- III. Anwar Ali, Björn Redfors, Joel Lundgren, Jessica Alkhoury, Jonatan Oras, Li-Ming Gan, Omerovic E. **The role of heart rate in isoprenaline-induced takotsubo-like cardiac dysfunction in rats.** Europ J Heart Fail. 2020 July 20.
- IV. Anwar Ali, Björn Redfors, Jessica Alkhoury, Jonatan Oras, Li-Ming Gan, Omerovic E. **Sacubitril/valsartan decreases mortality and attenuates development of apical akinesia in rat model of isoprenaline-induced Takotsubo-like syndrome.** In manuscript.

# Pathophysiology and treatment of Takotsubo Syndrome

## Insights from preclinical studies

Anwar Gasim Elsieid

Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg,  
Sweden 2020

### ABSTRACT

**Background:** Takotsubo syndrome (TTS), also recognized as “stress-induced cardiomyopathy (SIC)” and “broken heart syndrome”, is an acute cardiac failure syndrome characterized by transient regional ventricular akinesia or hypokinesia, and often presents similarly to acute myocardial infarction (AMI). Unlike AMI, the characteristic regional myocardial akinesia in TTS does not involve a culprit coronary artery. Although the associated cardiac dysfunction is potentially reversible, TTS is no longer regarded as benign. Today we know that TTS can lead to deleterious complications including death. Because physical and/or emotional stress often precedes TTS, acute sympathetic stimulation is believed to play a central role in pathogenesis of TTS, but the detailed mechanisms are still unclear. There are no clinical randomized studies in patients with TTS. Therefore, we currently lack guidelines for treatment.

**Aims:** The aims of this thesis were to study the reproducibility of our rat model, to unravel TTS pathophysiology and to explore possible prevention and treatment strategies in TTS. We aimed to investigate whether exogenous catecholamines can induce TTS-like cardiac dysfunction in rats.

**Methods:** We used 10-week-old Sprague Dawley rats in these preclinical studies. We based this work on our experimental TTS rat model which is based on exogenous isoprenaline. We tested whether different catecholamines, given intraperitoneally could induce TTS. We studied possible preventive roles of  $\beta$ -blockers, ivabradine, sacubitril/valsartan and cardiostimulants in our rat model. Blood pressure and heart rate were recorded via carotid artery cannulation. We used small animal echocardiography to study cardiac morphology and function, and collected cardiac tissues for histopathological studies.

**Results:** In **Study I**, we reproduced our isoprenaline-based rat model of TTS and showed that exogenous catecholamines can induce different patterns of TTS, depending on the associated blood pressure rather than their adrenergic receptor affinities. In **Study II**, we observed that phosphodiesterase inhibitor milrinone can induce typical TTS. We demonstrated that pretreatment with either  $\beta$ -non-selective antagonist or  $\beta$ 1-selective antagonist, but not  $\beta$ 2-selective antagonist, can prevent isoprenaline-induced TTS. Cardiostimulants failed to prevent isoprenaline-induced apical TTS. In fact, pretreatment with levosimendan worsened the degree of left ventricular apical akinesia. In **Study III**, we showed that ivabradine as well as heart block could prevent isoprenaline-induced TTS. Finally, in **Study IV**, we showed that pretreatment with sacubitril/valsartan can reduce mortality and prevent isoprenaline-induced TTS.

**Conclusion:** Our isoprenaline-based rat model of TTS is reproducible. Exogenous catecholamines can cause different variants of TTS depending on the associated haemodynamic profiles rather than catecholamine adrenergic receptor affinities. Hypotension and tachycardia precede isoprenaline-induced LV apical TTS in rats. Phenylephrine, ivabradine and  $\beta$ 1-selective antagonists could prevent typical TTS. These drugs mitigate the unique isoprenaline-associated haemodynamic profile. Takotsubo syndrome should, therefore, be regarded as an acute sympathetic stimulation-induced *haemo-neuro-cardiac* syndrome rather than a cardiomyopathy per se. Inotrope and cardiostimulants such as milrinone and levosimendan can be deleterious in TTS.

**Key words:** Takotsubo syndrome, milrinone, levosimendan, echocardiography, isoprenaline, sacubitril/valsartan, ivabradine, stress-induced cardiomyopathy.

ISBN 978-91-7833-980-8 (PRINT)

ISBN 978-91-7833-981-5 (PDF)

Printed by Stema Specialtryck AB, Borås

SAHLGRENKA AKADEMIN  
INSTITUTIONEN FÖR MEDICIN

