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Impact of Acute Stress on Regional Cerebral Metabolism and Metabolic Connectivity in Takotsubo Cardiomyopathy

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Extended Abstract

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, is triggered by acute stress, that causes an over-release of stress hormones such as catecholamines. This release leads to symptoms similar to a myocardial infarction but without coronary artery obstruction [1]. While previous research [2] by our group has highlighted metabolic, functional, and structural changes in the heart during TSS, the metabolic response of the brain to TTS stress has not been explored in this model. Our study investigated the regional metabolic response and metabolic inter-regional connectivity of the brain during TTS progression.

TTS was induced in female Wistar rats (n=5) through a single intraperitoneal injection of 50 mg/kg isoprenaline (ISO) [3]. Dynamic fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans were performed before stress (baseline), 2 hours (acute phase), and 7 days (recovery phase) post-ISO. The dynamic brain scans, covering up to a duration of 30 minutes post-FDG injection, were registered to a brain atlas developed by W. Schiffer [4], allowing the segmentation of the brain into 58 regions. Using the software PMOD and kinetic 2-tissue compartment FDG model, we calculated the kinetic constants of FDG inflow (K1), outflow (k2), and phosphorylation (k3) in the brain regions.

During the acute phase, a general decrease with respect to pre-stress values was observed in glucose perfusion (K1 and k2) and phosphorylation (k3) constants in most of brain regions and significant metabolic changes (p-value ≤ 0.05 in univariate t-tests) were observed in 65%, 67% and 49% of brain regions for K1, k2 and k3, respectively. During the recovery phase, perfusion constants remained decreased, but the phosphorylation constant generally exceeded pre-stress values. A metabolic correlation analysis (significant Pearson correlations with $|r| \geq 0.9$ and p-value ≤ 0.05) to quantify connections between regional brain metabolic constants revealed a remarkable interhemispheric perfusion hypoconnectivity during the acute phase with regards to pre-stress, followed by a perfusion hyperconnectivity during the recovery phase, indicating a synchronised dysregulation of long-term brain glucose flux. The connectivity modifications during the acute phase concerned mostly limbic and sensorimotor functional networks. In the limbic network, the total number of connections among regions changed with respect to pre-stress from 46 to 26, from 35 to 25, and from 13 to 21 for K1, k2, and k3, respectively. In the sensorimotor network, the corresponding numbers were 7 to 7, 5 to 0, and 7 to 9 connections. During the recovery phase, the number of connections inside the limbic network increased with respect to pre-stress and acute stress, reaching 95, 61 and 30 connections for K1, k2, and k3, respectively. In the sensorimotor network, numbers increased to 29 and 24 for K1 and k2 but decreased to 3 for k3.

These results demonstrate significant and lasting changes in brain glucose metabolism induced by an acute catecholaminergic stress, similar to triggers of TTS, with a marked impact on the connectivity and functionality of the limbic

and sensorimotor systems. Observing cerebral metabolic dysregulation in a reproducible animal model of TTS provides insights for future research on TTS's complex neurological implications.

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