Mini Review

Interventional Cardiology

The role of insulin and glucose handling in Takotsubo syndrome

Abstract

Takotsubo Syndrome (TTS), also known as stress-cardiomyopathy or broken-heart syndrome, is an acute heart failure condition typically triggered by severe stress. Patients present with symptoms resembling acute myocardial infarction but without coronary artery obstruction. Evidence from animal and human studies suggests that impaired glucose handling and transient insulin resistance are key elements in TTS, with significant implications for cardiac function. Here we aim to accentuate the importance of glucose metabolism in both acute and long-term TTS outcome, suggesting that modulating glucose uptake and overcoming insulin resistance may be a crucial therapeutic strategy.

Keywords: Takotsubo syndrome • Broken heart syndrome • Acute heart failure • Insulin

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Introduction

Takotsubo Syndrome (TTS), also known as stress-cardiomyopathy or broken-heart-syndrome, is a form of Acute Heart Failure (AHF), which is often triggered by severe physical or emotional stress. It mimics symptoms of acute myocardial infarction, like chest pain and shortness of breath, but without proof of coronary artery obstruction in coronary angiography [1]. The condition frequently begins after experiencing an emotional or physical stressor, leading to its alternative names, 'stress cardiomyopathy' or 'broken-heart syndrome'. Characterized by a temporary change in form and function of the heart's left ventricle, it is usually reversible with most patients recovering from the acute event within a short time frame. The most common type of presentation includes apical ballooning and basal hyper contractility of the left ventricle. Contrary to earlier beliefs that considered TTS a relatively harmless condition, recent evidence shows that TTS is not a benign disease as previously assumed but is associated with impaired short- and long-term outcome [2]. Long-term follow-up of patients with TTS showed that the annual mortality rate from any cause was 5.6% per patient, while the annual occurrence of significant adverse cardiac and cerebrovascular events stood at 9.9% per patient. Unfortunately, to this day, there is no specific pathophysiology-driven evidence-based treatment [3]. The underlying mechanisms of the disease are only partly understood and catecholamine-driven Insulin Resistance (IR) and myocardial inflammation are suggested to play an important role in the pathogenesis of TTS.

Literature Review

Recently published data from our group shows that elevated glucose plasma levels in TTS patients on presentation to the emergency department may predict impaired intra-hospital outcome [4]. Plasma glucose levels are associated with elevated myocardial damage, heart rate, left ventricular end-diastolic pressure, C-reactive protein, leukocyte count, peak high-sensitive Troponin T, reduced left ventricular ejection fraction

and elevated intra-hospital mortality. Also TTS patients with higher plasma glucose required intra-hospital catecholamine use, respiratory support, and/or resuscitation more frequently. Recent prospective data from a longer follow-up of TTS patients shows that patients with hyperglycemia on admission have a higher risk of heart failure or death after 24 months [5]. At hospitalization, patients with high blood sugar compared to those with normal blood sugar exhibited elevated levels of inflammatory markers and B-type natriuretic peptide, along with a decreased left ventricular ejection fraction. Additionally, there was a correlation between glucose levels and norepinephrine concentrations. Interestingly, diabetes mellitus has even been discussed as a potential protective comorbidity in TTS as several studies have reported low prevalence and rates of diabetes in patients with TTS [6]. This hypothesis has been labeled the 'diabetes paradox' [7], potentially explicable by diabetes-associated neuropathy with subsequently impaired cardiac sympathetic innervation and a diminished response to catecholamines. However, diabetes has been convincingly shown to be associated with impaired outcome in TTS in a larger clinical study, showing significantly increased mortality over a 2.5-year follow-up in TTS patients with diabetes. Furthermore, diabetes was recognized as an independent factor predicting worse health outcome [8], and is part of the InterTAK prognostic score, indicating elevated 5-year mortality [9]. Taken together, higher glucose levels and diabetes indicate impaired short- and long-term outcome in TTS, which also yields the question of HbA1c as a potentially useful follow-up parameter for risk stratification in future clinical studies. Elevated HbA1c levels in patients who presented with newly identified glucose abnormalities were linked to a substantial decrease in survival following invasive treatment for acute myocardial infarction. Furthermore, in individuals with impaired glucose tolerance and newly diagnosed diabetes mellitus, a rise in HbA1c was among the most potent independent predictors of mortality [10].

With respect to pathophysiology, elevated glucose may mirror increased sympathetic drive as TTS is often triggered through emotional or physical distress [11]. Interestingly, glucose infusion lowers plasma adrenaline and the production of thromboxane A2 in the paraventricular nucleus of hypothalamus [12]. Positron Emission Tomography (PET) data shows that patients suffering from TTS experience reduced glucose uptake in certain myocardial segments [13-15]. These abnormalities in metabolism are mainly located in the apical and para-apical segments [16], the regions most affected by wall motion abnormalities in TTS [17]. The diminished uptake of the [18], F-fluorodeoxyglucose tracer during the acute stage of TTS is often described as the "metabolic trapping effect." This refers to the temporary retention of glucose in the heart tissue, which does not proceed to further metabolic processing. Also, follow-up imaging by PET can unmask TTS and help exclude the differential diagnosis of acute coronary syndrome [19]. In an Isoprenaline (ISO) based rat model of TTS, glucose and lipid metabolic pathways were dysregulated with decreases in final glycolytic and β-oxidation metabolites. An increase in myocardial glucose uptake led to the buildup of sugar phosphates in the early stages of glycolysis, along with a marked increase in metabolites that signify different end products of the glucose metabolism. Yet, despite an overall elevation in the gene/protein expression related to the glycolytic process, there was a decreased presence of the end metabolites of glycolysis, specifically lactate and pyruvate. Thus, defective Ca2+ handling, inflammation and upregulation of remodeling pathways were suggested due to energy carrier deficit [20]. In female rats ISO-induced TTS-like heart failure revealed long-term metabolic reprogramming in the heart, progressing towards metabolic dysfunction, ultimately culminating in irreversible impairment of cardiac function and structure [21]. In human-induced pluripotent stem cell-derived cardiomyocytes treated with ISO and high dose glucose the expression of PI3K/Akt, β1-adrenoceptors, Gs-protein, and PKA were decreased, indicating a beneficial effect of high glucose with respect to catecholamine toxicity [22]. In mice with EPI-induced TTS, insulin- and glucose treatment improved ejection fraction and survival while myocardial expression of pro-inflammatory markers as well as myocardial damage were markedly reduced. In line with these findings, a decrease in the expression of left ventricular chemokines and cytokines, such as il-1β, il-6, and ccl2 could be observed. Additionally, the expression of brain natriuretic peptide was blunted following treatment with insulin but not glucose, compared to EPI4.

Taken together these results suggest that an important issue in TTS may be Insulin Resistance (IR) rather than the detrimental effects of high glucose levels per se. Also, overcoming IR may be a therapeutic strategy in TTS that remains to be explored. In line with this hypothesis, Madias, et al., proposed Glucose-Insulin-Potassium (GIK) for the management of TTS [23]. In two patients with TTS insulin was administered and the results in terms of metabolic effects and impact on cardiac performance were encouraging, indicating potential benefits and underscoring the need for additional research to further validate this treatment approach [24,25]. In patients with acute myocardial infarction the usage of GIK is investigated and results from a first study showed that a composite outcome of cardiac arrest or in-hospital mortality could be detected less often in patients receiving GIK infusion. Furthermore the beneficial mechanisms of insulin on cardiac function, including improved contractility [26], and cardiac output [27], with elevated glucose uptake in catecholamine-mediated myocardial IR [28,29], highlight the necessity for further studies to understand the underlying mechanisms and potential therapeutic implications.

For patients with heart failure with reduced ejection fraction the current standard of care includes an angiotensin receptor/neprilysin inhibitor, a beta-blocker, a mineralocorticoid receptor antagonist, and a Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitor [30]. While lowering glucose by osmotic diuresis appears counterproductive with respect to the aforementioned findings in TTS, SGLT2 inhibitors enhance the myocardial usage of glucose and fatty acids while ameliorating myocardial inflammation [31,32], and may therefore be beneficial for TTS patients nevertheless. In our mouse model of TTS, we observed a pivotal contribution of calcineurin-driven myocardial inflammation. Analysis of gene sets in heart tissue RNA sequencing post-EPI injection indicated a significant upregulation of gene networks related to calcineurin-induced inflammation. This effect was more evident in male mice compared to female mice, aligning with the observed gender differences in the mouse model's characteristics. Elevated regulator of calcineurin 1-4 (rcan1-4) expression was also observed in the peripheral mononuclear blood cells of TTS patients, hinting at the syndrome's systemic impact. Prophylactic and therapeutic administration of calcineurin inhibitors, specifically cyclosporine and tacrolimus, in mice treated with EPI led to improved cardiac function and reduced myocardial injury. These results point to calcineurin inhibition as a potential treatment strategy for TTS, which will be further investigated in the Cyclosporine in Takotsubo Syndrome trial (CIT, NCT05946772). In this regard, insulin also ameliorated myocardial cytokine expression upon experimental TTS which may in part explain its therapeutical benefit.

Conclusion

The pathophysiology of TTS is complex. Studies in both animals and humans indicate a crucial role of glucose metabolism in TTS. IR emerges as a potential therapeutic target, with beneficial effects of insulin in animal models. While data on insulin use in TTS patients is limited, preliminary results are optimistic. A better understanding of myocardial glucose metabolism and its modulation in TTS may be essential for optimal treatment of TTS patients.

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