International Journal of Cardiology 222 (2016) 874–880

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Acute, repetitive and chronic Takotsubo syndrome in patients with chronic kidney disease: Sympathetic reno-cardial syndrome

Shams Y-Hassan

Karolinska University Hospital, Huddinge, Department of Cardiology, S-141 86 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 2 May 2016
Received in revised form 18 July 2016
Accepted 30 July 2016
Available online 2 August 2016

Keywords:
Takotsubo
Chronic kidney disease
Dialysis
Heart failure
Sympathetic
Cardio-renal disease

ABSTRACT

Heart failure and cardiovascular death are common in patients with chronic kidney disease (CKD) and extremely prevalent in patients undergoing dialysis. It has been shown that the excess of cardiovascular mortality in this patient population is not fully accounted for by the traditional cardiovascular risk factors. Substantial evidence exists for the presence of sympathetic over-activity in patients with dialytic and non-dialytic CKD. Several studies have also been reported on reversible segmental left ventricular wall motion abnormality consistent with myocardial stunning in association with dialysis especially hemodialysis. In the literature, the most acceptable underpinning hypothesis for the myocardial stunning in CKD is "demand myocardial ischemia". However, the occurrence of cardiac sympathetic over-activation-disruption and repeated reversible myocardial stunning in patients with CKD can be compared to that occurring in acute Takotsubo syndrome where local cardiac sympathetic disruption may cause acute regional circumferential pattern of myocardial stunning. In this manuscript, converging evidences suggestive for the fact that acute, repetitive, and chronic TS may be one of the important causes of cardiac morbidity including myocardial stunning and heart failure and mortality in patients with CKD are provided.

1. Introduction

Takotsubo syndrome (TS), also known as broken heart syndrome and cardiac sympathetic disruption syndrome or neurogenic stunned myocardium, is currently a well-recognized and increasingly reported acute cardiac disease entity [1–3]. The disease is characterized by a presentation resembling that of acute coronary syndrome (ACS) and a peculiar type of circumferential typically regional left ventricular wall motion abnormality (LVWMA) resulting in a conspicuous ballooning of the left ventricle during systole. Invasive coronary angiography does not show a coronary culprit lesion, which can explain the whole observed LVWMA. The term "Takotsubo" was introduced by Sato and Dote in 1990 to describe the silhouette of the left ventricle during systole in patients presenting with clinical features of myocardial infarction and no obstructive coronary artery disease [4,5]. Takotsubo, which is a Japanese term, is a pot with a round base and narrow neck used in Japan for trapping octopuses (Tako = octopus and Tsubo = pot). The disease is often triggered by an emotional or physical stress factor. Among the physical stress factors are acute and chronic kidney diseases (CKD) [6,7].

Different varieties of renal diseases seem to have the ability to stimulate the afferent signaling through sensory renal nerves. These afferent signals are centrally integrated and result in sympathetic outflow directed toward the diseased kidneys in an attempt to restore appropriate perfusion. At the same time, the sympathetic outflow is also directed toward other organs like the heart and the blood vessels to improve the perfusion of the injured kidneys. These are compensatory mechanisms, which are necessary in order to restore the normal physiology of the affected organs. However, when the process continues and leads to over-activation of the sympathetic nervous system, it may have deleterious effects on the affected organs as kidneys and the heart. This initiates three vicious circles as depicted in Fig. 1 causing among others repeated myocardial stunning resulting in heart failure with increased morbidity and mortality. Recently, we have provided sufficient evidence that chronic TS with acute exacerbation may be the main pathogenesis for the increased morbidity and mortality in patients with decompensated chronic heart failure without chronic kidney disease [8–10].

In fact, the essentiality of the sympathetic nervous system activity for the body organs including the kidneys and the heart and the dreaded damages that it can cause during over-activation-disruption may be compared to the indispensable importance of water for the life on the earth and the damages the water can cause during water intruding. Water leakage can cause rotting of wood, rusting of steel and delaminating of materials such as plywood and many others as the sympathetic nerve over-activity in predisposed patients may cause sympathetic nerve terminal disruption and norepinephrine spillover resulting in myocardial stunning and cardiac damage.

Patient with CKD have a 30-fold increase in mortality (higher risk for dialysis patients) than age-matched controls [11]. The excess of

E-mail address: shams.younis-hassan@karolinska.se.

http://dx.doi.org/10.1016/j.ijcard.2016.07.278
0167-5273/

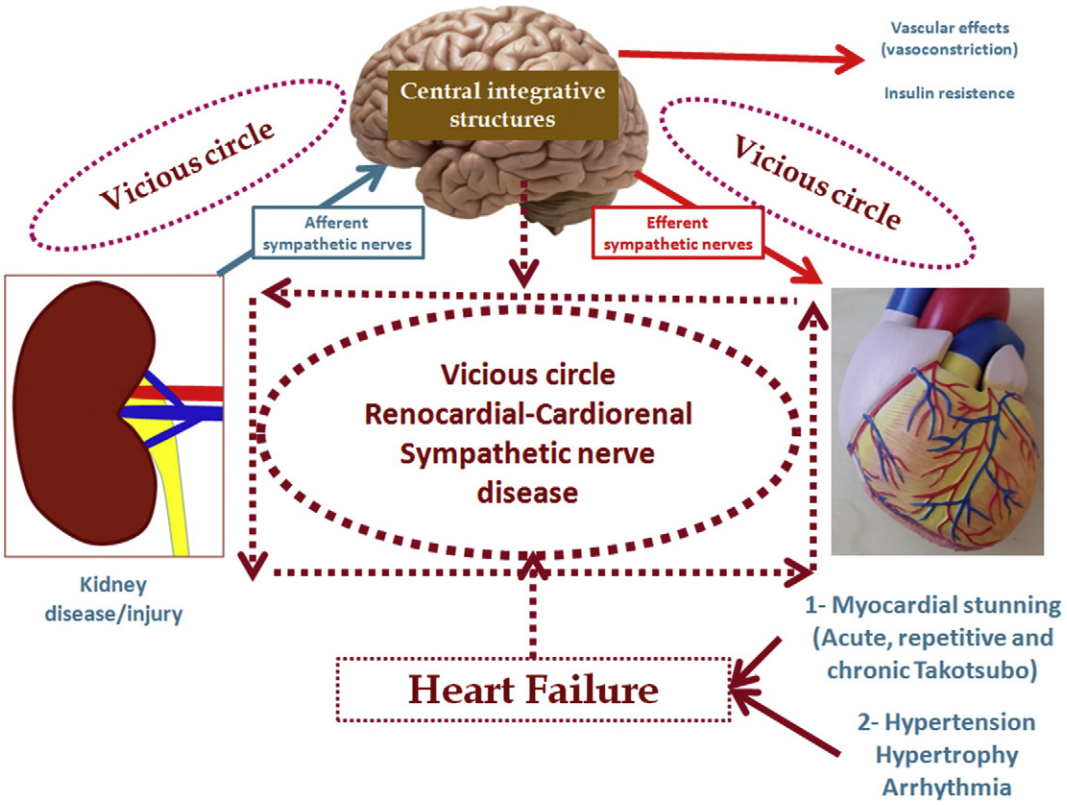

Fig. 1. Reno-cardial sympathetic nervous disease. Acute and chronic renal diseases initiate stimulation of sensory afferent nerves fibers signaling to central integrative structures in the brain. This results in increased efferent sympathetic outflow to target organs including the heart, kidneys, vasculatures and other organs. The excessive sympathetic outflow affects the heart through causing hypertension with left ventricular hypertrophy and through repeated myocardial stunning (acute, repetitive and chronic Takotsubo syndrome). With time, three vicious circles (Renal-Brain, Brain-Heart and Renal-Brain-Heart) as shown in the figure result in progressive heart failure with its consequences.

cardiovascular morbidity and mortality in patients with dialytic and non-dialytic CKD cannot be accounted for by an increase in the traditional risk factors and coronary artery disease. Overwhelming evidences exist supporting the hypothesis that the kidneys can be both generators and recipients of increased sympathetic nervous system activity [12]. Researchers in this field have demonstrated signs of significant increase in sympathetic nerve activity assessed by measuring increased muscle sympathetic nerve activity (MSNA) and plasma norepinephrine in patients with CKD [13]. Other researchers have demonstrated repetitive regional myocardial stunning in patients with renal failure especially those undergoing hemodialysis [14]. The myocardial stunning occurs even in patients with renal failure and no underlying coronary artery disease and in pediatric population on dialysis treatment [11]. In the literature, the most accepted underpinning hypothesis for the myocardial stunning in CKD is the "demand myocardial ischemia". So far, no investigator has tried to link the increased cardiac sympathetic activity with local cardiac sympathetic disruption and norepinephrine seethe and spillover to the occurrence of myocardial stunning in CKD. Critical review of the pathogenesis of TS displays a scenario resembling that happening in reno-cardial syndrome in patients with CKD. In this manuscript, substantial evidences for the similarities between clinical presentation, course, and the event sequences in the pathogenesis of acute TS and that of reno-cardial syndrome in CKD are provided and summarized in Table 1.

2. Pathogenesis

2.1. Trigger and predisposing factors

2.1.1. Takotsubo syndrome

In about 70% of patients with TS, the disease is preceded by an emotional or a physical stress factor [15]. Among the physical stress factors, which merit to be mentioned in this context, are the acute and dialytic and non-dialytic CKD [6,7].

The most common predisposing factor for TS is the elderly female gender. Eighty to 90% of patients in TS are postmenopausal women [15]. Burgdorf et al. [16] found that the prevalence of cancer was high among patients with TS (23.6%), which greatly exceeded the expected prevalence of cancer in age-matched populations in the United States (8.2%) and all European countries combined (7.8%). Sharkey et al. [2] assessed prospectively the clinical profile and outcome of 136 consecutive patients with TS and showed that TS was a marker for increased non-cardiac mortality. Citro et al. [17] have showed seasonal (peak at summer and nadir at autumn) and diurnal (peak at the morning and nadir at the night) variation of the TS onset. This may signify a potential link between seasonal and diurnal TS onset and the underlying pathophysiologic mechanisms. The frequency of chronic anxiety disorders was significantly greater in patients with TS in another study [18]. Recently, Pelliccia et al. [7] have demonstrated that patients with TS are associated with some comorbidities. The most common comorbidities were psychological disorders, pulmonary diseases, malignancies, neurologic diseases, chronic kidney diseases and thyroid diseases.

2.1.2. Reno-cardial syndrome

Patients with CKD are exposed to many stress factors as that associated with different types of dialysis, which may lead to acute exaggerated sympathetic nervous activity including local renal and cardiac sympathetic over-activation. It is known that CKD is one of the important co-morbidities associated with TS [7] and may predispose to repeated myocardial stunning in association acute renal disease exacerbation or hemodialysis.