Mechanisms of Stress (Takotsubo) Cardiomyopathy

Sebastian Szardien, MD[a,*], Helge Möllmann, MD[a,b], Matthias Willmer, MD[a], Yoshihiro J. Akashi, MD[c], Christian W. Hamm, MD[a,b], Holger M. Nef, MD[a,b]

KEYWORDS

• Stress cardiomyopathy • Takotsubo cardiomyopathy • Catecholamines • Contractile dysfunction

KEY POINTS

- Stress cardiomyopathy (SCM) is a form of reversible systolic dysfunction of the mid and apical left ventricle with pathologic changes of the electrocardiogram in absence of an obstructive coronary artery disease.
- The prevalence of SCM among patients with symptoms suggestive of myocardial infarction is 0.7% to 2.5%, and it is found predominantly in postmenopausal women (90%).
- No large studies have confirmed the etiology of SCM so far.

INTRODUCTION

Since awareness has developed of cardiac SCM, also known as takotsubo cardiomyopathy, transient apical ballooning, or broken heart syndrome, stress has become known as a major risk factor for cardiovascular morbidity and mortality.[1–4] It was first described by Dote and colleagues,[2] who named it, *takotsubo*, because the shape of the left ventricle resembles a Japanese octopus trap, with a round bottom and narrow neck. SCM is characterized by a reversible systolic dysfunction of the mid and apical segments of the left ventricle. Most commonly, postmenopausal women are affected.[5] Symptoms occur after emotional or physical stress and are similar to those seen in acute myocardial infarction, including sudden onset of chest pain associated with convex ST segment elevation and a moderate increase in creatine kinase and troponin levels.[5–7] A diagnosis of obstructive coronary artery disease can be excluded, however, in the presence of severely depressed left ventricular function. Variant forms of left ventricular dysfunction have been reported, including wall-motion abnormalities, such as midventricular ballooning with sparing of the basal and apical segments or inverted Takotsubo.[8–10] Involvement of the right ventricle is common in SCM and associated with more severe left ventricular dysfunction.[11,12] Any form of contractile dysfunction is transient and reversible with resolution generally achieved within days or weeks.[1,7] The prognosis of SCM is favorable,[6] although fatal complications, such as cardiogenic shock, malignant arrhythmias, and free wall rupture of the left ventricle, have been reported.[13–16] The in-hospital disease-related mortality rate is 2% to 4%.[17,18] Although patients with SCM have a higher 4-year cardiovascular survival compared with people from the general population matched for age and gender, an association with malignancies has been demonstrated in approximately 50 patients.[17,19] No large studies have yet confirmed the cause of stress cardiomyopathy.

[a] Department of Cardiology, Kerckhoff Heart and Thorax Center, Benekestrasse 2-8, Bad Nauheim 61231, Germany; [b] Medical Department I, Cardiology, University of Giessen, Klinikstr. 33, 35392 Gießen, Germany; [c] Division of Cardiology, Department of Internal Medicine, St Marianna University School of Medicine, 2-16-1 Sugao Miyamae-ku, Kawasaki-city, Kanagawa-prefecture 216-8511, Japan
* Corresponding author. Department of Cardiology, Kerckhoff Heart and Thorax Center, Benekestrasse 2-8, Bad Nauheim 61231, Germany.
E-mail address: s.szardien@kerckhoff-fgi.de

Heart Failure Clin 9 (2013) 197–205
http://dx.doi.org/10.1016/j.hfc.2012.12.012
1551-7136/13/$ – see front matter

HISTORICAL PATHOPHYSIOLOGIC CONCEPTS OF SCM

Several pathophysiologic concepts of SCM have been discussed in the past years. Recent research data, however, cast most of these hypotheses in doubt.

In the early stage of research activity, several investigators assumed a regional limited myocarditis as cause of SCM. Myocarditis-specific alterations, however, were excluded in numerous myocardial biopsies. Furthermore, inflammatory markers are classically not elevated in SCM and most patients do not have a history of previous infectious diseases.[1,20]

For a long time, multiple coronary vasospasms and the occurrence of SCM have been closely linked.[2] Larger cohort data, however, revealed coronary vasospasms in only 1.4% of patients with SCM.[7] In further studies, it has been tested whether vasospasms could be provoked pharmacologically in patients with SCM. Even in these studies, spontaneous vasospasms were observed in only 2% of patients and the percentage of pharmacologic provoked vasospasms varied from 0% to 43% of patients[1,6,21]; a recent meta-analysis revealed that coronary vasospasms were provocative in 27.6% of cases.[22] In summary, multiple vasospasms are unlikely to be the major trigger of SCM.

In some patients, an obstruction of the left ventricular outflow tract has been observed in the acute phase of SCM.[23,24] Therefore, it has been postulated that this obstruction may be caused by a catecholamine-induced hyperkinesia of the basal segments thereby leading to apical ballooning, which in turn leads to an impaired coronary perfusion by increased wall tension.[25] This may explain the observed regional wall abnormalities, ECG changes, and increased biomarkers.[25] Larger studies could not confirm this hypothesis, however, because in many patients no significant pressure gradient was observed.[26]

SCM is still a diagnosis by exclusion.

MORPHOLOGIC ALTERATIONS IN SCM

In recent studies, morphologic and ultrastructural alterations in SCM have been characterized systemically.[11,27] In the acute phase, a significant loss of the contractile proteins, actin and myosin, can be observed. The contractile material is partially restricted to the peripheral zone of the cell with a disarrangement of myocytes. The cytoskeletal proteins, α-actinin and titin, are significantly reduced in the acute phase of SCM, leading to changes in sarcomeric length, dissociation of myofibrils, and disturbances of the interaction between myofibrils (**Fig. 1**). The resulting functional consequence of these alterations is a reduction of contraction efficiency and relaxation capacity. A complete restoration of this myocyte arrangement can be observed after functional recovery.

Apart from the contractile apparatus, the extracellular space shows remarkable alterations. The acute phase of SCM is accompanied by an accumulation of cardiac fibroblasts and myofibroblasts.[11] Accordingly, a significant enlargement of the extracellular matrix with increased protein expression of collagen I, collagen III, and fibronectin can be observed (**Fig. 2**). The functional consequence of this enlargement of the extracellular matrix, besides a reduced systolic contraction, is an intracellular and extracellular uncoupling with consecutive affection and loss of the syncytium. After functional recovery, the amount of the extracellular proteins reveals a clear trend toward regression.[11]

TRANSCRIPTIONAL PROFILING IN SCM

After processing human biopsies, a complete transcriptional profile of patients with SCM was described for the first time in 2008.[28] Most notably, a group of genes that are controlled by the transcription factor, nuclear factor E2–related factor (Nrf-2), are significantly up-regulated during the acute phase of SCM. The Nrf-2–induced transcription plays an important role in the early cellular response to oxidative stress. Several of these Nrf-2–induced genes are involved in the so-called redox signaling.

Several genes directly controlling cellular translation are significantly up-regulated in the acute phase. In particular, ribosomal proteins 6 and 9 show a significantly increased expression. The so-called female genes are strongly expressed in the acute phase, which, given that mostly postmenopausal women are affected, is interesting.

After functional recovery, particularly mitochondrial genes as well as genes involved in respiratory chain, citrate cyle, and β-oxidation showed a significant up-regulation. Hence, signaling pathways and mechanisms responsible for energy generation in the cell in particular seem to be crucially important during the recovery phase.

DISTURBANCES OF MICROCIRCULATION

In patients with SCM, disturbances of myocardial microcirculation in the apical and midventricular myocardium were detected by using positron emission tomography, which were reversible after