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A proposal for a noninvasive monitoring of sympathetic nerve activity in patients with takotsubo syndrome

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ABSTRACT

The pathophysiology of takotsubo syndrome (TTS) is still elusive; many hypotheses of its cause have been proposed with a heightened activity of the peripheral autonomic sympathetic nervous system (PASNS) via local norepinephrine release, and direct cardiomyocyte toxicity mediated by blood-borne catecholamines, being among the most currently entertained. Monitoring of PASNS during hospitalization will provide a metric which could be of immense value in unraveling of the pathophysiology and aiding in the management of the patients with TTS by predicting in-hospital complications, long-term outcome, and its recurrence. Recent work with noninvasive monitoring of skin sympathetic nerve activity (SKNA), via conventional electrodes used for the recording of the electrocardiogram have shown that the filtered signals > 500 Hz originate in the cervical and stellate ganglia, which also innervate the heart, and thus they provide an estimate of stellate ganglion nerve activity. Such information may prove invaluable for the management of patients with TTS.

The pathophysiology of takotsubo syndrome (TTS) continues to be elusive; epicardial and microvasular spasm, microcirculation dysfunction, aborted myocardial infarction, left ventricular outflow tract obstruction, epinephrine-induced switch in signal trafficking, unbridled direct stimulation of the heart by the peripheral autonomic sympathetic nervous system (PASNS) via local norepinephrine release, direct cardiomyocyte toxicity mediated by blood-borne catecholamines, increase in the myocardial energy demands, estrogen deficiency, and endothelial dysfunction are some of the pathoetiological mechanisms for TTS, currently entertained [1–6]. The pathophysiology of TTS is complex, and various sets of its putative mechanisms are discussed by different workers; thus some emphasize the role of the extent of circulating catecholamines, extreme sympathetic activation of the cognitive centers of the brain and hypothalamic-pituitary adrenal axis, and the cardiac and vascular responses to severe stress [7]; another points out that pathology similar to TTS has been repeatedly reported in the literature prior to its formal description in 1990 and 1991, and there is a wealth of clinical studies and animal experiments revealing the role of intense activation of the central nervous system (CNS), sympathetic nervous system, and circulating catecholamines in triggering such pathology [8]; some others stress that although the “clinical and epidemiological features of TTS have been well characterized, the main pathophysiological mechanism and prognostic consequences of TTC remain largely unknown” [9]; and others focus on the large array of CNS disorders, e.g., subarachnoid bleeding, epilepsy, ischemic stroke, migraine, intracerebral bleeding posterior reversible encephalopathy syndrome, amyotrophic lateral sclerosis, encephalitis, or traumatic brain or spinal cord injury, often trigger TTS [10].

It is not clear to what extent the activation of the CNS and PASNS, which had triggered the TTS phenotype, continue to perpetuate further myocardial stunning, or after instigating the myocardial insult they are now less contributory to further damage. Of course there is evidence that hyperactivity of certain CNS regions (e.g., basal ganglia, hippocampus, and brainstem), and hypoactivity of the prefrontal brain cortex, as assessed by their regional blood flow rate (an index of their functional activity) persist in the subacute phase of TTS, way past the time of full restoration of normal myocardial function [11]. Also elevated catecholamines have been documented in serial measurements during hospitalization of patients with TTS [3], although this finding has not been reproduced in several other studies, which have shown either normal or mild to moderate elevation of epinephrine and metanephrine [4,12–14], and mild to moderate elevation of norepinephrine and normetanephrine [14]. Indeed as per these latter findings, catecholamines are unlikely to be the trigger for the initiation of the TTS pathogenetic process, and when elevated may reflect the underlying cardiogenic shock or heart failure in some patients with TTS [14]. Also it is thought that elevated cantecholamines (innately secreted, or externally administered) instead of inducing TTS, may act as a trigger for

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the cardiac sympathetic system hyperactivation, which in turn causes TTS [15]. Although some parasympathetic influences appear to be evident in the subacute phase of TTS's clinical presentation, leading to bradycardia hypotension, and atrio-ventricular blocks [2], it is the hyperactivity of the sympathetic nervous system that has preeminence in triggering the TTS phenotype [1,2,4,13]. The role of the CNS in generating the sympathetic surge and conveying it, via the PASNS, to the cardiomyocytes, is paramount to the pathogenesis of TTS. Various emotional and physical stressors occurring in the setting of normal living, or in the course of a large array of illnesses (sepsis, intracranial bleeding, stroke, seizures, asthma, perioperative and peri-anesthesia states, etc) comprise the substrate for the CNS to initiate the sympathetic seethe cascading in the intense activation of the PASNS, and mediating the insult to the cardiomyocytes [4]. The emergence of TTS after emotional upheavals or physical stresses, the associated circumferential pattern of ventricular stunning, which parallels the distribution of the sympathetic cardiac nerves, the cardiac denervation detected by sintigraphic iodine-123-meta-iodobenzylguanidine (MIBG) imaging, in the course of TTS, the extensive animal experimentation associating brain lesions with cardiac lesions or ventricular dysfunction and with a cardioprotective effect exerted by sympathectomy, but not adrenalectomy, are some of the many points comprehensively elaborated in a recent review on the pathophysiology of TTS [4], which bespeak of the prime role of CNS and PASNS in mediating TTS. A recently reported insight associating TTS in patients with a lower prevalence of diabetes mellitus, than the general population, and attributed to a "cardioprotective" influence of PASNS diabetic neuropathy [16], indirectly supports the pathogenetic role of PASNS in TTS. Consequently, monitoring these CNS and PASNS hyperactivities may be of value in unraveling the pathophysiology of TTS (both triggering and perpetuation), and in explaining the time course of recovery, morbidity and mortality during hospitalization, and recurrence of TTS at follow-up. Indeed such monitoring may be useful as we contemplate pharmacology to "pacify" the CNS, and employ β-blockers to attenuate or neutralize the injurious influence of the heightened cardiac stimulation, and prevention of TTS recurrence. Although evaluating serially the CNS (upstream effect) [11] may not be currently feasible or practical, the PASNS (downstream effect) may be amenable to monitoring, employing various modalities.

A crude way to monitor the heightened activity of the PASNS in patients with TTS is by serially evaluating for hypertension and/or tachycardia. Also the activity status of PASNS can be assessed in the subacute and follow-up phases of TTS, by the noninvasive techniques of chronotropic response and heart rate recovery, during and after exercise stress testing, assessment of baroreflex function, ambulatory electrocardiography (ECG)-based heart rate variability, Valsalva maneuver, cold water pressor test, and even invasive microneurography. However some of the above modalities are indirect, require a laboratory environment, are invasive, may be cumbersome, requiring an active/contributing role by the tested patients, and thus do not lent themselves to implementation in the acute phase of TTS, when stressed patients are admitted and cared for in an intensive care unit (ICU). Also the patients with acute/subacute TTS undergo a series of required invasive and noninvasive diagnostic and therapeutic procedures (transthoracic echocardiography, coronary angiography, cardiac magnetic resonance imaging, frequent blood laboratory testing, and implementation of extracorporeal membrane oxygenator). Accordingly, what is needed is a noninvasive technology reliably and directly monitoring the activation status of PASNS, in the context of a busy and involved existence of the patients admitted to the ICU with suspected or proven TTS. Such technology not only is expected to provide data in parallel to other metrics monitored serially, but also to be useful for the initiation, dosing, therapeutic response monitoring, or discontinuation of drug therapy (e.g., β-blockers). Also this monitoring technology could inform us about the continuous role (or its absence) of PASNS in the progression of disease, emergence or amelioration of complications (e.g., new myocardial regional wall contraction abnormalities, mitral regurgitation, and left ventricular outflow tract obstruction), length of the recovery course, and early and late recurrence of TTS.

There is such potentially suitable technology presently available for the noninvasive monitoring of skin sympathetic nerve activity (SKNA), with all the desired attributes outlined above, for implementation in patients with TTS [17–20]. This method employs conventional ECG electrodes, and provides simultaneous monitoring of the SKNA and the ECG, by high-pass filtering of recorded skin signals for SKNA, and low-pass filtering for the ECG. It is rooted in the realization that SKNA, recorded in the thorax and upper extremities, originate in the cervical and stellate ganglia, which also innervate the heart, and thus it provides an estimate of stellate ganglion nerve activity [17–20]. The current version of the technology has evolved from previous work with subcutaneous nerve activity recordings in ambulatory animals. In these experiments the amplitude (measured in μV) and morphology of sympathetic nerve activity signals paralleled those of the stellate ganglia, and both nerve activities correlated with heart rate acceleration, and preceded the onset of arrhythmias. Also left cervical vagal nerve stimulation has reduced sympathetic SKNA activity in patients with drug resistant epilepsy [19], suggesting that the latter reflects sympathetic nerve activity expressed in the thorax and upper extremities. Thus the SKNA activity, from the high pass filtered signals, considered as "noise" when the focus is on the ECG recordings, can be used as a good estimate of sympathetic nerve activity, emanating from the stellate ganglia, innervating the heart [17]. The authors of the paper cited herein [17], have shown that SKNA recordings, via conventional ECG electrodes, can be reliably acquired from conventional limb and precordial ECG electrodes (Fig. 1). Recently this SKNA method has been employed in a study of 56 subjects (healthy volunteers, epileptic patients without known cardiac disease, patients with history of implanted cardioverter-defibrillator shock therapies for ventricular storms [≥3 episodes of ventricular tachycardia {VT} or ventricular fibrillation per 24 h], and patients undergoing bilateral stellate ganglion lidocaine injection). In a series of elegant experiments the associations of the increased SKNA with Valsalva maneuver, cold water pressor test, heart rate rise, QTc interval lengthening, emergence of VT episodes, and the effect of the lidocaine stellate ganglion injections, were studied. SKNA rise and fall correlated with imposed Valsalva maneuver and subsequent recovery, and cold water pressor test (with the associated heart rate change often less well correlated with SKNA), in the normal volunteers. Heart rate acceleration and lengthening of the QTc interval correlated with SKNA rise in the epileptic subjects, as shown previously with sympathetic stimulation in normal controls. Episodes of documented sustained and non-sustained monomorphic and polymorphic VT were preceded by a rise in SKNA, in the patients with history of ventricular storms. Finally the lidocaine stellate ganglion injections were associated with significant initial rise of SKNA, while the needle was inserted under fluoroscopic guidance and local contrast injection was delivered to identify the location of the stellate ganglia, with reduction of SKNA after the lidocaine injection. More recent work in 11 patients with this technology showed that a rise in SKNA preceded episodes of atrial tachycardia and atrial fibrillation (AF), and correlated with the number of such episodes, and the sinus rate in the individual patients, with the latter 2 having a reciprocal relationship, suggestive of a sinus node remodeling induced by the recurrent episodes of AF [18]. Also 6 patients with drug-resistant epilepsy, who were admitted for video electroencephalographic monitoring, were treated previously with vagal nerve stimulation, and showed statistically significant decrease in their SKNA, and heart rate, in comparison with 20 control similar patients who did not receive prior vagal nerve stimulation [19]. The above suggest that SKNA, recorded via conventional ECG electrodes, can be taken as a surrogate of stellate ganglion nerve activity, and an index of the intensity of the PASNS input to the heart [17–20].

This new method of SKNA recording could potentially have a significant role, in monitoring patients with TTS. Here are some relevant