International Journal of Cardiology 176 (2014) 1–5

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Editorial

Coronary vasospasm is an unlikely cause of Takotsubo syndrome, although we should keep an open mind

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ARTICLE INFO

Article history:
Received 30 April 2014
Accepted 29 June 2014
Available online 5 July 2014

Keywords:
Takotsubo syndrome
Pathogenesis of Takotsubo syndrome
Coronary vasospasm
Coronary vasospasm provocative testing
Microvascular dysfunction

ABSTRACT

This viewpoint pertains to the still elusive pathophysiology of the Takotsubo syndrome (TTS), maintaining the position that this affliction is not the result of coronary vasospasm (CV) involving one or more coronary arteries. Although CV has been rarely encountered in the acute stage of TTS, or elicited via provocative testing in the subacute stage of the disease, it does not appear to be the cause of TTS as shown by the bulk of the published relevant literature. The author provides some speculations to explain the spontaneous appearance of CV, or its artificial elicitation, in some patients with TTS. However while we are striving to unravel the pathophysiology of TTS, we should keep an open mind about a possible role for CV in the causation of TTS.

In a recent Editorial Tobis [1] highlights Takotsubo syndrome (TTS), emphasizing that the pathophysiology of this affliction is still elusive, outlines a plan for an international repository and registry of cases of TTS, and calls the community of interventional cardiologists to action, to unravel the cause(s) of this mysterious disease. This indeed is a laudable prospect and attempts to spur our interventional colleagues, who are the ones called upon to decipher early in the clinical course of patients admitted with symptoms/signs of acute coronary syndrome (ACS), either due to the common coronary atherosclerotic substrate with destabilized fissured or eroded coronary plaques and/or thrombosis, or to the allegedly uncommon TTS, whatever is its cause. Tobis refers specifically to the work of Angelini, of the Texas Heart Institute, who maintains that TTS is due to an intense coronary vasospasm (CV) of all of the major epicardial coronary vessels, based on his findings of demonstrated CV following acetylcholine testing (AchT) in such patients. Importantly contribution to the proposed registry can be accommodated for investigators who will, or will not, employ acetylcholine infusions during coronary arteriography (COAR) of their patients with TTS.

I have studied the reports by Angelini et al. pertaining to TTS, at the time of their appearance, and more recently, I have found the following: 1) in a patient with bronchogenic carcinoma, Prinzmetal's angina, associated with CV of the left anterior descending coronary artery, and neurocardiogenic syncope [2], who most probably had TTS, all symptoms evanesced immediately after the start of chemotherapy and irradiation, and the authors attributed them to paraneoplastic manifestations. Incidentally in a large number of reports, TTS has been associated with malignancy, which is attributed to both paraneoplastic influences [3] and elevated sympathetic nervous system tone, associated with the emotional and physical stresses of patients due to the diagnosis of malignancy, and the administered therapies [3,4]. This prompted other investigators and Angelini to recommend evaluations for malignancy of patients presenting with TTS, with the disease considered a paraneoplastic manifestation [4], or a neurocardiogenic syndrome [5]. 2) Angelini described 4 patients with TTS, who underwent AchT, which revealed that this condition is "caused by severe, sustained CV of many or all of the coronary vessels" [6]; in one of these patients, CV occurred during AchT with echocardiography (ECHO)-derived evidence of the left ventricular apical ballooning typical of TTS, and in two other patients AchT provoked CV and TTS suggestive symptoms, prompting the author to theorize that TTS is a form of Prinzmetal's angina of relatively longer duration, and recommending delayed (5–30 days) AchT to "be routinely performed under specific, prospective, investigational protocols at specialized centers" [6]. Of interest is that patient #1 of this report had a normal nuclear sestamibi myocardial perfusion imaging acutely, and apical hypoperfusion 24 h later; also AchT induced diffuse CV relieved by nitroglycerine, which was provoked during the subacute phase, several days after admission with TTS [6]. 3) Angelini [7], and Lyon et al. [8], exchanged letters in response to the latter's report that TTS is mediated by elevated epinephrine levels [9], with the former proposing diffuse CV as a cause for TTS, emphasizing that such spasticity is transient and occurs in

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http://dx.doi.org/10.1016/j.ijcard.2014.06.069
0167-5273/

susceptible individuals with "preexisting endothelial dysfunction", explaining the inconsistency of results, among other cited reasons, for the AchT to provoke CV in patients with TTS [7]. Lyon et al. [8] countered that TTS is due to "direct negative inotropic effects of supraphysiological epinephrine levels upon the myocardium mediated via the β2 adrenoceptor, with an apical-basal β adrenoceptor density gradient determining preferential apical stunning"; they agreed that an interaction of the catecholamine surges with endothelial dysfunction may be at play, but they doubted that inducible diffuse CV represents the underlying cause of TTS, but rather a surrogate marker of abnormal coronary endothelial function in the aftermath of high catecholamine levels. 4) Angelini commented [10] about a published case report of a patient with TTS in the setting of an electrophysiological procedure [11], citing his group's previous experience with AchT in TTS. 5) Angelini presented the case of a patient with midventricular TTS who underwent AchT several days after recurrent episodes of chest pains, which responded to nitroglycerin, and attributed this variant of TTS to selective CV of diagonal, ramus intermedius, and obtuse marginal branches of the circumflex coronary artery, with sparing of the left anterior descending coronary artery [12]; he again emphasized the interplay of triggers of varying intensity, with coronary artery endothelial dysfunction of varying degree. 6) Angelini [13] commented on two cases of inverse TTS presented by Lee et al. [14], citing his previous experience with AchT in this disease, urging clinicians to implement AchT prior to discharge of patients with TTS, stating that he has not encountered patients with the inverse TTS variant, and referring to a spectrum of pathology ranging from Prinzmetal's angina to TTS. 7) Angelini [15] commented on a paper by Manzalal et al. [16], describing 3 patients with inverse TTS, again extolling the merits of AchT, referring to the response of chest pain to nitroglycerine, calcium blockers, and L-arginine, in patients under testing, indicating that he "had seen approximately 200 cases of TTC at his institution but none clearly identifiable as isolated reverse TTC," and concluding that "the distribution of the impaired myocardial function to the basal segments of the left ventricle in reverse TTC suggests that the predominant active pathways in an episode of TTC initially involve neurologic [17], as well as vascular (endothelial) dysfunction [15]". Angelini et al. [18] presented a case of a patient with biventricular TTS, evidence of distal CV of the left anterior descending and right coronary artery branches at AchT 15 days after the onset of TTS, with simultaneous ECHO-based proof of apical left and right myocardial akinesis with prompt response to nitroglycerin, and full recovery and uneventful follow-up on an upgraded therapy of nitrates, calcium blockers, and L-arginine, with further comments emphasizing that TTS is due to an interplay of some triggers with a transiently segmental epicardial (or microvascular?) coronary impairment of endothelial function, demonstrated by AchT, and responding to nitroglycerine. In summary, Angelini et al. [2,5–7,10,12,13,15,18] view TTS as a form of Prinzmetal's angina, varying from the latter only in its longer duration, with CV affecting all or different coronary arteries, either in their totality or in their distal ramifications, reproducible during AchT, responsive to nitroglycerine, and based on a state of transient segmental endothelial dysfunction.

The pathophysiology of TTS is still elusive. We know that TTS is not due to epicardial obstructive coronary artery disease of the type producing the clinical manifestations of ACS, based on COAR employed to differentiate these 2 conditions, or due to myocarditis leading to a diffuse hypokinetic cardiac state, since TTS is a transient segmental mainly akinetic/dyskinetic state affecting the left and/or right ventricles due to unknown mechanism(s), while myocarditis is associated with some particulars inherent to its presence. However more work is needed to define specific diagnostic criteria for myocarditis, which will enable clinicians to differentiate it from TTS in the acute and subacute phases of these 2 pathological entities. It is conceivable that the inciting mechanism(s) in TTS is(are) operating only briefly causing the affliction, which then runs its course, or continue(s) to be influential at the time of clinical presentation of the patients with invariant or diminishing intensity, or that there is(are) different mechanism(s) at play leading to the emergence and impacting the maintenance of TTS. Accordingly it could be envisaged, for example, that there is segmental ischemia of a few minutes in duration (probably longer than what is encountered in Prinzmetal's angina), resulting from CV at the epicardial coronary and/or arteriolar level(s) in TTS, which has evanesced by the time the patients undergo evaluation at the hospital, where a state of segmental myocardial stunning is witnessed, with or without evidence of coronary microcirculatory dysfunction, akin to spontaneous, or percutaneous coronary intervention-related myocardial perfusion injury, in the setting of ACS. Indeed it may be revealing to evaluate the microcirculation substrate of patients with suspected TTS in the acute setting, immediately after establishing the patency of each of the 3 coronary arteries, by assessing their corresponding microcirculation resistance index [19], or employing COAR-, or ECHO-based methodologies for the evaluation of the microcirculation (TIMI angiographic grades and count frames, or ECHO myocardial contrast, correspondingly). It is humbling, but we should accept the notion, that we may not be able to detect the inciting early mechanism(s) of TTS, and thus relevant progress could be only made with reliance on pathogenesis-seeking animal models of the disease. However there is a window of opportunity for gaining some valuable insights during the time that preparations for COAR are under way, provided that TTS along with the more common ACS is being considered in the differential diagnosis, for both inpatients and patients presenting to the Emergency Department, for exploring of regional myocardial wall motion abnormalities (RWMAs), their evolution, and their impact on the overall left ventricular ejection fraction. This will require a drastic change in our mindset and currently prevailing "culture", since what is advocated herein is not a referral for a single formal transthoracic ECHO after COAR, but a repeatedly performed, even cursory, ECHO by various members of the care providing team, employing hand-held ECHO devices [20]. In addition, this will require a formal Doppler sophisticated ECHO interrogation, for impairment of the left anterior descending coronary artery coronary flow reserve early after admission, and not during the initial 48 h, as previously reported [21]. Further aid with differential diagnosis can be provided by serial blood sampling for cardiac biomarkers, brain natriuretic peptide, and catecholamines, and frequent recording of the electrocardiogram; in regard to the later, attenuated voltage of the QRS complexes present on admission, or developing during the initial 24 h, may have some sensitivity and specificity for TTS [22], and may become facilitated in the near future by smart phones, cloud computing and storage of patients' health data, enabling clinicians to compare the admission ECG with previous tracings of a patient recorded anywhere in the world [23].

It has been hypothesized that TTS is due to any of the following: 1) transient diffuse, or single vessel-based CV of the epicardial coronary artery and/or corresponding arteriolar bed [6,24–35]; 2) unbridled autonomic, mainly sympathetic (but also parasympathetic) cardiac nerve stimulation with resultant cardiomyocyte toxicity, engendered by local norepinephrine release [36]; 3) blood-borne norepinephrine (other catecholamines?) injurious influence on the cardiomyocytes [37]; 4) blood-borne epinephrine (mainly released from adrenals)-mediated stimulation of the altered β2 myocardial adrenergic receptors via a switch from Gs to Gi proteins [9,38]; 5) catecholamine-induced basal ventricular hyperkinesis with the development of intracardiac pressure gradients and resultant damage to the "unprepared" midventricular and apical myocardium [39,40]; and 6) catecholamine-induced regional mechanical overload and demand/supply mismatch in selected ventricular regions, and metabolic shutdown with resultant protective acute down regulation of nonvital cellular functions to prevent necrosis [41,42]. Of course it is also conceivable that 2 or more of the above cited pathophysiological mechanisms could be operating in concert, and to a changing degree (dynamic interaction) during the acute phase of the illness, to induce and maintain the