Reader's Comments: Subclinical Hypothyroidism and the Risk of Cardiovascular Disease

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Dear Sir,—We highly appreciated the long-term study by Moon et al on the substantial increased risk of ischemic cerebrovascular and cardiac events in individuals younger than 65 years old with subclinical hypothyroidism.[1] We wish to draw the attention to a curable mechanism driving this association, that is the infection by pathogenic strains of *Helicobacter pylori (H. pylori)*. Such organisms are marked by the production of the cytotoxin-associated gene A protein (CagA) and are endowed with an increased inflammatory potential. The infection by CagA positive *H. pylori* strains has been associated with several autoimmune diseases, including autoimmune thyroiditis, and disorders that recognize in the inflammatory response an important pathogenetic event.[2] *H. pylori* is well known for its ability to mimic human antigens, and to elicit autoantibodies against cells of several organs, including the thyrocyte. Autoimmune thyroid diseases are sustained by elevated proinflammatory cytokine levels, namely interleukin-6 and tumor necrosis factor-alpha, which are strongly elevated by infection with *H. pylori* expressing CagA.[3] These same cytokines can promote premature myocardial infarction and ischemic stroke, pathologies that are likewise associated with infection the pathogenic strains of *H. pylori*.[4] Not last, infection by this pathogen can induce lymphoid accumulation in the stomach, a phenomenon that is strictly similar the lymphoid infiltration in the gland of patients with Hashimoto thyroiditis. The variability with which subclinical hypothyroidism is associated with stroke and premature myocardial infarction in different studies might well depend on the highly variable circulation of pathogenic strains in different areas. These strains are far more prevalent in Asian and South American countries than in the US.

Disclosures

None of the authors has anything to disclose.

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Some Thoughts About the Different Ballooning Patterns in Patients With Recurrent Takotsubo Syndrome from the Ones During Their Index Takotsubo Episode

Perusal of the 4,204 articles, published in PubMed from its inception to February 23, 2019, accessed in response to MeSH term "takotsubo," reveals that Takotsubo syndrome (TTS) occasionally recurs in some patients, and such recurrence emerges within days, weeks or years (sometimes >10), after the index TTS episode.[1–3] A parallel observation deriving from the same source is that the ballooning pattern affecting the left and/or right ventricle(s) displays different "regionality" in the index and the recurrent TTS episodes.[1–3] Thus, while the patient was found for example, to have an apical ballooning during the index illness, as assessed by echocardiography, contrast ventriculography, or cardiac magnetic resonance imaging, the left basal ventricular, or the left mid-ventricular myocardial territory, or any combination of the above, is/are found during the recurrent TTS episode. The identified regional contraction abnormalities in TTS are apical, mid-ventricular, basal (i.e., reverse or inverse TTS), focal, global, and right ventricular, and any combination of the above.[1–3] An associated issue is the TTS-triggering stressful condition, which has been identified to be emotional or physical in nature, (herein one wonders whether it is possible for a patient to suffer a physical stress completely devoid of an emotional overlay), although a sizeable proportion of patients have suffered TTS in the absence of any identifiable inciting stressful patient experience. It has been observed that the recurrent TTS episodes may be triggered by the stressors of the same or different nature, as the index TTS episodes.[1]

Although the pathophysiology of TTS is still elusive, compelling insights attribute the emergence of this illness to an unbridled autonomic sympathetic nervous system seethe and/or blood-borne catecholamines flooding the circulation, from adrenal hypersecretion.[1–3]

The occurrence of the frequent apical ballooning pattern in patients with TTS has been attributed to a higher β-adrenergic receptor density at the apex than at the base, shown in dog experiments,[4] but not demonstrated in humans,[5] resulting in a more intense adrenergic stimulation of the apical than the basal myocardium. What has been shown in humans is an increased sympathetic innervations of the heart's base compared with the apex,[6] functionally compensated by a larger β-adrenergic receptor density in the apex than the base.[4] Additionally the sympathetic innervation is more dense in the anterior than in the inferior left ventricle in humans,[6] which explains the more frequent anterior than inferior regional wall motion abnormalities in patients with TTS. Another postulated pathophysiological mechanism resulting in TTS, which has been explored in a rat model,[7] was shown to precipitate an adrenergic apical stimulation of β_2-adrenoceptors, with a shift from the canonical Gs (stimulating)-, to a Gi (inhibiting)-based signal transduction, leading to cardiodepressant/cardioprotective effects on the myocardium, during the catecholamine assault. Some of the above pathomechanisms, lead to an as yet not completely understood complex autonomic adrenergic neural input to the human heart (cardiomyocytes and/

or coronary circulation), and/or injurious influences of elevated and/or altered in regional sensitivity circulating catecholamines, to result in the different ballooning patterns seen in human TTS.[5]

In a recent report from the International Takotsubo (InterTak) Registry investigators,[8] 66 patients (4.7%) among the 1,402 were observed to have suffered recurrent TTS after the index episode, at 30 days to 9.9 years of follow-up, with some developing more than one recurrences. There was no association of TTS recurrence with gender, but patients with neurological or psychiatric afflictions had a predilection for ≥1 TTS recurrences. Interestingly, 34.8% of patients revealed a different ballooning pattern in the index and recurrent TTS episode, prompting the authors to doubt the often cited proposal that an apical/basal gradient of sympathetic innervation and reverse β-adrenoceptor densities are at the pathophysiological roots of regional contraction phenotypes of TTS. Instead the authors, based on their findings, believe "that an activation of different central pathways affecting different parts of the myocardium and/or the coronary microcirculation might be responsible for the pathogenesis in TTS".[8] Indeed the primacy of a role for starting the TTS cascade can be traced to the activation and suppression of specific brain regions, as assessed by regional cerebral blood flow changes,[9–11] or evidence of a dysfunctional limbic system and a hypoconnectivity of central brain regions essential for integration of the autonomic function.[12,13] Although it appears that a hyperactivated autonomic sympathetic nervous system and flooding of blood catecholamines play a role in the excessive stimulation of cardiomyocytes in patients with TTS, 59.6% of patients who suffered recurrent TTS in the above cited study,[8] were taking β-blockers, with 84.6% of them taking β_1-blockers, suggesting that such drugs may not prevent TTS recurrence. Whether this paradox is due to the enormity of stressors, overwhelming the protective effects of β-blocking drugs triggering TTS, or an upregulation of cardiac β-adrenergic receptors (engendered regionally or globally), by the chronic β-blocker therapy, has not as yet been determined.

But what is the mechanism of the different myocardial regions (e.g., midventricular) in recurrent TTS as compared with the territories (e.g, apical) involved during the index TTS episode? One could speculate that the different ballooning patterns during recurrent TTS as compared with the index TTS episode could be traced to: (1) emotional versus physical triggers eliciting the 2, and this could be explored in the 66 patients with recurrent TTS from the InterTaK Registry[8]; (2) this in turn could be associated to pathological alterations of different brain regions, precipitating the index versus the recurrent TTS episodes, which could be explored with modalities discussed above[9–13]; (3) dissipation over time of the "memory effect" invoked by some[14] to "protect" myocardial regions previously involved in the TTS index episode, through a "phenomenon analogous to regional ischemic preconditioning"; (4) accordingly, recurrent TTS episodes occurring a few weeks and months after an index TTS episodes could involve different myocardial territories, due to the "memory" effect, while recurrent TTS episodes occurring after years could involve the same myocardial regions as the index TTS episodes in the same patients, due to the dissipation of the "memory" effect; (5) this hypothesis could be probably explored in the 66 patients of the InterTak Registry with recurrent TTS; (6) the "protective" effect observed in a previously involved myocardial region during recurrent TTS could be probably traced to lingering underlying autonomic sympathetic denervation exerted by the index TTS episode, and persisting for 1 to 2 years, observed in studies employing serial ^{123}I-mIBG imaging,[15] with such denervation "protecting" previously involved regions for the first to the second year after the index TTS episode, but not later; (7) accordingly, recurrent TTS occurring up to ~2 years would involve myocardial areas other than the ones impacted during the index TTS episodes, while recurrent TTS occurring beyond ~2 years could involve the same territories afflicted during the index TTS episodes, which in the meantime have been reinervated; (8) this could be shown by ^{123}I-mIBG imaging,[15] of patients with recurrent TTS, who had such imaging during their index TTS episode.

Disclosures

Nothing to disclose.

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Characteristics, Outcomes, and Predictors of Significant Pericardial Complications in Patients who Underwent Transcatheter Aortic Valve Implantation

Large pericardial effusion and cardiac tamponade are known periprocedural complications of Transcatheter Aortic Valve Implantation (TAVR).[1,2] Pericardial complications have also been associated with increased morbidity and mortality in patients who underwent permanent pacemaker insertion and percutaneous coronary intervention.[2–4] This study describes characteristics, outcomes, and predictors of patients who develop significant pericardial complications related to TAVR.

For our analysis, we included all patients who underwent TAVR (ICD 9 DM 35.05 and 35.06) in the National Inpatient Sample database from 2012 to 2014. We excluded those patients who underwent other procedures that might cause pericardial complications. Our primary outcome of interest was significant pericardial complication, defined as a composite of cardiac tamponade (ICD 9 DM 42.33), pericardiocentesis (ICD 9 DM 37.0), or pericardial window (ICD 9 DM 37.12). We performed multivariable regression analysis on predictors of significant pericardial complications.

Between 2012 and 2014, 41,025 patients underwent TAVR. After exclusions, 34,820 were included in our

Table
Baseline characteristics and inhospital outcomes of patients with significant pericardial complications versus those without

Variables	Significant pericardial complication N = 465 (%)	No significant pericardial complication N = 34,355 (%)	p value
Age	82.9 ± 8.5	81.1 ± 8.5	<0.001
Female	340 (73.1)	16385 (47.7)	<0.001
Caucasian versus other race	370 (85.1)	27985 (87.7)	0.46
Hypertension	365 (78.5)	27450 (79.9)	0.75
Diabetes mellitus	110 (23.7)	11820 (34.4)	0.035
Congestive heart failure	30 (6.5)	4045 (11.8)	0.11
Chronic pulmonary disease	130 (28)	11575 (33.7)	0.227
Renal failure	165 (35.5)	12120 (35.3)	0.966
Obesity	55 (11.8)	4820 (14)	0.531
Anemia	130 (28)	9020 (26.3)	0.701
Coagulopathy	160 (34.4)	8090 (23.5)	0.015
Liver disease	<11*	880 (2.6)	0.805
Weight loss or underweight	65(14.0)	1665(4.8)	<0.001
Chronic malnutrition	35(7.5)	900(2.6)	0.003
Fluid and electrolyte imbalance	180(38.7)	8895(25.9)	.005
Coronary artery disease	255 (54.8)	24395 (71)	0.001
History of tobacco use	105 (22.6)	9745 (28.4)	0.211
History of PCI	55 (11.8)	6595 (19.2)	0.057
History of CABG	30 (6.5)	7990 (23.3)	<0.001
History of valve replacement	<11*	495 (1.4)	.227
Cardiac implantable electronic devices	20 (4.3)	5185 (15.1)	0.004
Teaching hospital	400 (86)	30470 (88.7)	0.452
Rural hospital	<11*	265 (0.8)	0.713
Elective versus non-elective admission	355 (76.3)	26785 (78)	0.676
Transapical TAVR	65 (14.0)	6430 (18.7)	0.266
Cardiac arrest	75 (16.1)	930 (2.7)	<0.001
Cardiogenic shock	40 (8.6)	910 (2.6)	<0.001
Respiratory failure	180 (38.7)	7015 (20.4)	<0.001
Acute renal failure	115 (24.7)	5935 (17.3)	0.063
Hemorrhage	40 (8.6)	1390 (4)	0.019
Acute renal failure+hemodialysis	20 (4.3)	550 (1.6)	0.04
Discharge to skilled nursing facility	170 (36.6)	9825 (28.6)	0.085
Mortality	115 (24.7)	1130 (3.3)	<0.001
Length of hospital stay (days) (IQR)	9(0−20)	6(2−10)	<0.001

PCI = Percutaneous coronary intervention: CABG = Coronary artery bypass grafting