

Heart and lung, a dangerous liaison-Tako-tsubo cardiomyopathy and respiratory diseases: A systematic review

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Abstract

AIM: To investigate the possible association between Tako-tsubo cardiomyopathy (TTC)-a reversible clinical condition mimicking an acute myocardial infarction characterized by multifactorial pathophysiologic mecha-

nisms- and respiratory system diseases.

METHODS: We systematically searched PubMed and EMBASE medical information sources, to identify the different triggering causes, limiting our search to articles in English. The search keywords were: "tako-tsubo cardiomyopathy", "takotsubo", "takotsubo cardiomyopathy", "broken heart syndrome", "stress-induced cardiomyopathy", "apical ballooning syndrome", and "apical cardiomyopathy in combination with respiratory diseases, lung, pulmonary disease. For each kind of disease, we registered: author, year and country of study, patient sex, age, concurring situation, and outcome.

RESULTS: Out of a total of 1725 articles found, we selected 37 papers reporting a total of 38 patients. As expected, most patients were women (81.6%), mean age was 65 ± 10 years. Outcome was favorable in 100% of cases, and all the patients have been discharged uneventfully in a few days.

CONCLUSION: An association between respiratory diseases and TTC is likely to exist. Patients with severe respiratory diseases, due to the high dosages of β_2 -agonists used or to the need of invasive procedures, are highly exposed to the risk of developing TTC.

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Key words: Tako-tsubo cardiomyopathy; Stress cardiomyopathy; Respiratory diseases; Lung; Chronic obstructive pulmonary disease; Asthma

Core tip: This is the first study evaluating the association between respiratory diseases and Tako-Tsubo cardiomyopathy (TTC). Patients with severe respiratory diseases, due to the high dosages of β_2 -agonists used or to the need of invasive procedures, are highly ex-

posed to the risk of developing TTC. Thus, in these patients a certain caution should be maintained, along with a special alertness in suspecting and recognizing this particular disease.

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INTRODUCTION

Tako-tsubo cardiomyopathy (broken heart syndrome)

Tako-Tsubo cardiomyopathy (TTC) is a reversible clinical condition mimicking an acute myocardial infarction (AMI)^[1]. The original Japanese term “tako-tsubo” indicates the particular shape of the end-systolic left ventricle in ventriculography resembling that of the round-bottom and narrow-neck pot used for trapping octopuses^[2]. Other terms have been used to define this cardiac entity, *i.e.*, “apical ballooning”, “acute stress cardiomyopathy” or “broken heart”. Typical presentation involves chest pain and/or dyspnea, transient ST-segment elevation on the electrocardiogram (ECG), and a modest increase in cardiac troponin^[3].

The Mayo clinic diagnostic criteria include: (1) transient hypokinesis, akinesis or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and, frequently but not always, a stressful trigger; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin and, and (4) absence of myocarditis or pheochromocytoma^[1].

Although TTC is still underdiagnosed, the current prevalence estimate is approximately 1% to 3% (even 6% to 9% in women) of all acute coronary syndromes^[4]. The mean age ranges from around 60 to 75 years, both in men and women^[5], but its occurrence is much more likely (approximately 90%) in postmenopausal women^[6]. After a first finding on a large cohort of patients in Italy^[7], a precise temporal periodicity has been reported, characterized by highest occurrence peaks during morning hours and summer months^[8-9]. Interestingly, quite similar to AMI, Monday seems to be a critical day for onset^[10].

Even if TTC is frequently characterized by dramatic clinical presentation and urgent presentation to the Emergency Department, the prognosis is generally favorable, with a rapid short-term improvement of left ventricle systolic function^[11]. According to several studies, in-hospital mortality rates range from 0% to 8%^[4], with higher mortality rates for males than females^[12].

Multifactorial pathophysiologic mechanisms are likely to be involved, but the most accepted pathogenic hypothesis considers a rapid elevation of circulating catecholamine, triggered by emotional and/or physical stress, as a key mechanism^[13-14]. In fact, the major determinants of sympathetically mediated myocardial reversible dysfunction in patients with TTC include all the direct effects of catecholamines upon the myocardium, *i.e.* cellular damage, contraction band necrosis, defects in perfusion, altered cellular metabolism, and negative inotropic effects of epinephrine *via* stimulation of the cardioprotective β_2 -adrenergic receptors-Gi signaling pathway^[15]. It has been recently shown that the apical ventricular region has a greater $\beta_2:\beta_1$ adrenoceptor ratio, with a higher responsiveness and vulnerability to sympathetic stimulation^[16]. Again, the different occurrence of wall motion abnormalities could be explained by interindividual anatomical differences in the distribution of β -adrenergic receptors^[17,18].

Broken heart and broken lung: Is there a relationship?

The clinical onset of TTC is usually preceded by an emotional and/or physical stress with a similar distribution in approximately two-thirds of the patients. A long list of stressors has been reported, and this is continuously updated. Men seem to be more prone to physical stress and women to emotional stress^[19]. Among emotional stressors, for example, death or severe illness of a family member, receiving bad news, financial loss, move to a new residence, natural disasters, dispute or litigation, car accident, assault, surprise party, public speaking, and so on^[3]. Among physical stressors, surgery, cardiovascular procedures, medications and illicit drugs, and medical conditions, including gastroenterologic, endocrine, hematologic, renal, infectious, and neurologic diseases^[3]. Thus, we aimed to more-in-depth investigate the relationships between TTC and respiratory diseases.

MATERIALS AND METHODS

We systematically searched PubMed and EMBASE medical information sources, to identify the different triggering causes, limiting our search to articles in English. The search keywords were: “TTC”, “takotsubo”, “takotsubo cardiomyopathy”, “broken heart syndrome”, “stress-induced cardiomyopathy”, “apical ballooning syndrome” and “ampulla cardiomyopathy in combination with respiratory diseases, lung, pulmonary disease. Further papers were sought by means of manual search of secondary sources, including references from primary articles. For each kind of disease, we collected a set of data, including author, year of publication, country where the study was performed, and patient sex, age, concurring situation, and outcome.

RESULTS

Out of a total of 1725 articles found (1341 with the precise MeSH term (Takotsubo cardiomyopathy), we se-

Table 1 Respiratory symptoms or diseases and Tako-tsubo cardiomyopathy: Synopsis of published case reports

Symptom/disease	Gender, age (yr)	Concurring condition	TTC outcome	Country	Ref.
COPD					
Dyspnea	Female, 57	COPD	Favorable	United States	Pezzo <i>et al</i> ^[26]
Dyspnea	Female, 51	Unexpected death of her son COPD, Hypothyroidism Financial problems	Favorable	Poland	Bilan <i>et al</i> ^[27]
Status asthmaticus	Female, 66	COPD with multiple hospitalizations, heavy smoker	Favorable	United States	Rennyson <i>et al</i> ^[28]
Exacerbation	Female, 63	Multiple admissions	Favorable	United States	Makam <i>et al</i> ^[24]
Exacerbation	Male, 52	Financial unavailability to buy his drugs	Favorable	Spain	Pham <i>et al</i> ^[29]
Exacerbation	Female, 62	(1) COPD exacerbation (2) Family dispute (3) Acute thrombosis of aortobifemoral prosthesis	Favorable	Germany	Sager <i>et al</i> ^[30]
Exacerbation	Female, 68	COPD β2 agonist abuse	Favorable	Brazil	Salemi <i>et al</i> ^[21]
Exacerbation	Female, 63	Severe longstanding COPD, heavy smoker	Favorable	New Zealand	White <i>et al</i> ^[22]
	Male, 59	Ex-smoker, COPD Salbutamol abuse			
Exacerbation	Female, 76	COPD	Favorable	United States	Mendoza <i>et al</i> ^[23]
Exacerbation	Female, 63	β2 agonist abuse multiple exacerbations with noninvasive ventilation	Favorable	United States	Laktikova <i>et al</i> ^[25]
Asthma					
Bronchial asthma	Female, 74	Jet lag, 3 cups of coffee, 1-h sauna	Favorable	Taiwan	Chang <i>et al</i> ^[37]
Allergic rhinitis	Female, 84	Nasal decongestant abuse	Favorable	Brazil	Wang <i>et al</i> ^[34]
Status asthmaticus	Female, 46	Ketamine + epinephrine administration	Favorable	United States	Osuorji <i>et al</i> ^[33]
Bronchial asthma	Male, 72	Acute asthmatic attack	Favorable	Italy	Pontillo <i>et al</i> ^[31]
Suspected intractable bronchial asthma	Female, 62	Relapsing polychondritis	Favorable	Japan	Sato <i>et al</i> ^[35]
Allergic asthma	Male, 70	Allergy Cephalosporin use	Favorable	Italy	Santoro <i>et al</i> ^[36]
Asthma	Male, 53	Cocaine	Favorable	United States	Sarkar <i>et al</i> ^[38]
Status asthmaticus	Male, 50	b2 agonist abuse	Favorable	United States	Salahuddin <i>et al</i> ^[32]
Pulmonary embolism					
Pulmonary embolism	Female, 79	Long distance travel Popliteal vein thrombosis	Favorable	United States	Challa <i>et al</i> ^[42]
Pulmonary embolism	Female, 65	Pyelonephritis Emotional stress	Favorable	Italy	Fedele <i>et al</i> ^[41]
Malignancies, invasive procedures/surgery					
Cardiopulmonary bypass	Female	Mitral valve plasty	Favorable	Japan	Itoh <i>et al</i> ^[48]
Rigid bronchoscopy for debridement	Male, 77	Esophageal carcinoma + central airways invasion	Favorable	United States	Guerrero <i>et al</i> ^[50]
Intubation	Female, age not given	Parathyroid surgery (canceled)	Favorable	United States	Mueller <i>et al</i> ^[49]
Bronchoalveolar lavage	Male, 68	Fever and cough productive of sputum, history of tuberculosis	Favorable	South Korea	Ok <i>et al</i> ^[51]
Lung transplantation	Female, 55	End-stage lung fibrosis	Favorable	France	Michel-Cherqui <i>et al</i> ^[47]
Squamous carcinoma	Male, 51	Pulmonary resection	Favorable	South Korea	Lee <i>et al</i> ^[44]
Non-small cell lung cancer	Male, 72	Pulmonary resection	Favorable	Japan	Toyooka <i>et al</i> ^[45]
Lung adenocarcinoma	Male, 59	Heavy smoker, first diagnosis of malignancy with multiple metastases	Favorable	Turkey	Kepez <i>et al</i> ^[46]
Miscellaneous					
Cough	Female, 82	Bad coughing "pill went down the wrong way"	Favorable	United States	Butman <i>et al</i> ^[59]
Dyspnea	Female, 51	Diving (examination)	Favorable	France	Chenaitia <i>et al</i> ^[58]
<i>S. pneumoniae</i> pneumonia	Female, 65	Sepsis	Favorable	Australia	Geng <i>et al</i> ^[55]
Pulmonary edema	Female, 73	Frightening episode	Favorable	Northern Ireland	Daly <i>et al</i> ^[56]
Pulmonary edema	Female, 59	Motor-vehicle collision	Favorable	United States	Ritchie <i>et al</i> ^[57]
Pneumothorax	Female, 64	COPD	Favorable	United States	Kumar <i>et al</i> ^[52]
Pulmonary hypertension	Female, 69	Initiation of intravenous trepostinil	Favorable	United States	Cork <i>et al</i> ^[54]
Pulmonary hypertension	Female, 81	Right ventricular involvement	Favorable	Italy	Citro <i>et al</i> ^[53]
Smoking and "Venus"	Male, 81	Adulterous sexual intercourse	Favorable	Italy	Brunetti <i>et al</i> ^[60]

COPD: Chronic obstructive pulmonary disease. TTC: Tako-Tsubo cardiomyopathy.

lected 37 papers reporting a total of 38 patients (Table 1). As expected, most patients were women ($n = 31$, 81.6%),

mean age was 65 ± 10 years. Outcome was favorable in 100% of cases, and all the patients have been discharged uneventfully in a few days. As for country of origin, 15 studies (40.5%) were conducted in the United States, 5 (13.5%) in Italy, 3 (8.1%) in Japan, 2 (5.4%) each in Brazil, Korea and France, and one (2.7%) each in Poland, Spain, Northern Ireland, Germany, Turkey, Australia, Taiwan, and New Zealand.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is relatively frequently associated with TTC. In a retrospective analysis of a large cohort of approximately 17000 patients with diagnostic angiographies in Hamburg, Germany, Hertting *et al.*^[20], out of the 32 cases of TTC found that 14 (44%) had COPD or asthma. Since 72% of these patients were taking β -mimetics, the authors postulated that this kind of medication could have acted as preconditioning factor for the cardiomyopathy or aggravated the sympathetic nervous system stress. In fact, several other cases of TTC in patients with β -stimulators abuse have been reported^[21-23]. Multiple admissions for COPD exacerbations may act as a trigger^[24-25], alone or in combination with emotional stressors, *i.e.*, unexpected death of a son^[26], severe financial problems^[27-29], or family dispute^[30].

Asthma

Similarly to COPD, acute asthmatic attack may trigger TTC^[31], and pharmacological treatments may potentiate such an effect^[32-33]. Abuse of nasal decongestants in the course of allergic rhinitis has also been reported^[34]. TTC episodes have also been described in the case of relapsing polychondritis with symptoms of intractable bronchial asthma^[35], allergic asthma secondary to cephalosporin use^[36], abuse of coffee to cope with jet lag^[37], and also concomitant abuse of cocaine^[38]. In the latter case, the TTC cardiotoxic effect could have been potentiated by catecholamines^[39].

Pulmonary embolism

Arterial systemic embolization represents frequent complication during TTC. Mitsuma *et al.*^[40] studied the clinical characteristics and complications of 21 consecutive patients with TTC in Japan. Thromboembolism was found in 3 patients, 1 with ventricular thrombus and 2 with cardioembolic stroke. However, cases of pulmonary thromboembolism have been reported in elderly women as a consequence of acute pyelonephritis^[41], and a popliteal vein thrombosis after a long distance travel^[42].

Malignancies, invasive procedures and surgery

On the one hand, an association of TTC with malignancies has been hypothesized, potentially as a result of paraneoplastic phenomena^[43]. On the other, surgery and invasive procedures represent severe physical stressors capable to trigger TTC onset. Several cases of TTC events in patients with lung malignancies undergoing pulmonary resection have been reported^[44-46], and also after lung

transplantation for end-stage fibrosis^[47] or cardiopulmonary bypass^[48]. Again, other cases were associated with intubation^[49], debridement of central airways neoplastic invasion with rigid bronchoscopy^[50], and even after a simple bronchoalveolar lavage^[51].

Miscellaneous

Several other diseases or condition have been shown to trigger TTC. Among these, pneumothorax^[52], pulmonary hypertension^[53] also after attempt at treatment^[54], pneumonia with sepsis^[55], and pulmonary edema secondary to stressful events^[56,57]. A TTC episode occurred after acute dyspnea secondary to the stress of scuba diving in a 51-year-old woman (at the third immersion, as her level-3 diving examination), has been reported^[58]. Finally, 2 singular episodes of dyspnea occurred in ultraoctogenarians, both of them triggering a TTC episode: A bad coughing since “pill went down the wrong way” in a 82-year-old lady^[59], and a sudden dyspnea occurred in a 81-year-old man during an adulterous sexual intercourse with a young lady^[60].

DISCUSSION

If the question is: “Does an association between respiratory diseases and TTC exist” the answer is yes. On the one hand, patients with severe respiratory diseases, such as asthma or COPD, are exposed to a high risk of developing TTC in the course of critical exacerbations, when they are also compelled to assume high dosages of β -agonists. On the other hand, patients with lung cancer are often exposed to invasive procedures, both diagnostic and surgical, that may be relevant in predisposed subjects. Patients with acute respiratory symptoms or diseases should always be approached with caution in the event of invasive procedures or surgery, keeping in mind the possible acute cardiologic complications.

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COMMENTS

Background

Tako-Tsubo cardiomyopathy (TTC) is a reversible clinical condition mimicking an acute myocardial infarction. Its onset is characterized by multifactorial pathophysiologic mechanisms, and stress may play a crucial role.

Research frontiers

Patients with acute respiratory symptoms or diseases should be approached with caution in the event of invasive procedures or surgery, keeping in mind the possible acute cardiologic complications and the availability of managing abilities.

Innovations and breakthroughs

This is the first study evaluating the association between respiratory diseases and TTC.

Applications

More attention in either suspecting and recognizing TTC, and managing it.

Terminology

TTC is a reversible clinical condition mimicking an acute myocardial infarction. The original Japanese term "tako-tsubo" indicates the particular shape of the end-systolic left ventricle in ventriculography resembling that of the round-bottom and narrow-neck pot used for trapping octopuses.

Peer review

The authors have reviewed the association between respiratory diseases and Tako-Tsubo cardiomyopathy by searching case reports in world wide. They initially described general features of TTC, then discussed about relationship between TTC and respiratory disorders, including chronic obstructive pulmonary disease, asthma, pulmonary embolism, malignancies, invasive procedures, and miscellaneous. This article is well searched and summarized, and may provoke attention of TTC not only to cardiologists but also to pulmonologists and anesthesiologists.

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