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

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AIM: To investigate the possible association between Tako-tsubo cardiomyopathy (TTC)-a reversible clinical condition mimicking an acute myocardial infarction characterized by multifactorial pathophysiologic mechanisms- 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 "ampulla 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 β2-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 β2-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). 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. 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.

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.

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. The mean age ranges from around 60 to 75 years, both in men and women, but its occurrence is much more likely (approximately 90%) in postmenopausal women. After a first finding on a large cohort of patients in Italy, a precise temporal periodicity has been reported, characterized by highest occurrence peaks during morning hours and summer months. Interestingly, quite similar to AMI, Monday seems to be a critical day for onset.

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. According to several studies, in-hospital mortality rates range from 0% to 8%, with higher mortality rates for males than females.

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. 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-adrenergic receptors-G signaling pathway. It has been recently shown that the apical ventricular region has a greater β1-β2 adrenoceptor ratio, with a higher responsiveness and vulnerability to sympathetic stimulation. Again, the different occurrence of wall motion abnormalities could be explained by interindividual anatomical differences in the distribution of β-adrenergic receptors.

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. 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. Among physical stressors, surgery, cardiovascular procedures, medications and illicit drugs, and medical conditions, including gastroenterologic, endocrine, hematologic, renal, infectious, and neurologic diseases. 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            | Female, 57       | COPD                 | Favorable   | United States | Pezzo et al.  |
| Asthma          | Female, 57       | Male, 77, 3 cups of coffee, 1-h sauna | Favorable   | Taiwan | Chang et al.  |
| Dyspnea         | Female, 51       | COPD, Hypothyroidism | Favorable   | Poland | Bilan et al.  |
| Status asthmatic | Female, 66       | COPD with multiple hospitalizations, heavy smoker | Favorable   | United States | Remenyson et al.  |
| Status asthmatic | Male, 52         | Multiple admissions | Favorable   | Spain | Pham et al.  |
| Status asthmatic | Female, 62       | Financial unavailability to buy his drugs | Favorable   | Germany | Sager et al. |
| Asthma          | Female, 68       | COPD β2 agonist abuse | Favorable   | Brazil | Salemi et al.  |
| Asthma          | Female, 63       | Severe longstanding COPD, heavy smoker | Favorable   | New Zealand | White et al. |
| Asthma          | Male, 59         | Ex-smoker, COPD Salbutamol abuse | Favorable   | United States | Mendoza et al.  |
| Asthma          | Female, 66       | Acute asthmatic attack | Favorable   | Italy | Pontillo et al.  |
| Asthma          | Female, 63       | multiple exacerbations with noninvasive ventilation | Favorable   | United States | Laktikova et al.  |
| Asthma          | Male, 70         | Allergy Cephalosporin use | Favorable   | Italy | Santoro et al. |
| Status asthmatic | Male, 53         | Cocaine | Favorable   | United States | Sarkar et al. |
| Status asthmatic | Male, 50         | b2 agonist abuse | Favorable   | United States | Salabuddin et al. |
| Pulmonary embolism | Female, 79      | Long distance travel Pопliteal vein thrombosis | Favorable   | United States | Challa et al. |
| Pulmonary embolism | Female, 65      | Physical stress Pyleonephritis | Favorable   | Italy | Fedele et al.  |
| Malignancies. invasive procedures/surgery | Female, 57 | Mitral valve plasty | Favorable   | Japan | Itoh et al.  |
| Cardiopulmonary bypass | Male, 77 | Esophageal carcinoma + central airways invasion | Favorable   | United States | Guerrero et al. |
| Intubation      | Female, age not given | Parathyroid surgery (canceled) | Favorable   | United States | Mueller et al. |
| Bronchoalveolar lavage | Male, 68 | Fever and cough productive of sputum, history of tuberculosis | Favorable   | South Korea | Ok et al.  |
| Lung transplantation | Female, 55 | End-stage lung fibrosis | Favorable   | France | Michel-Cherqui et al.  |
| Squamous carcinoma | Male, 51 | Pulmonary resection | Favorable   | South Korea | Lee et al.  |
| Non-small cell lung cancer | Male, 52 | Pulmonary resection | Favorable   | Japan | Toyota et al. |
| Lung adenocarcinoma | Male, 59 | Heavy smoker, first diagnosis of malignancy with multiple metastases | Favorable   | Turkey | Kepez et al. |
| Miscellaneous   | Female, 82       | Bad coughing “pill went down the wrong way” | Favorable   | United States | Butman et al.  |
| Dyspnea         | Female, 51       | Diving (examination) | Favorable   | France | Cheranaita et al.  |
| S. pneumoniae pneumonia | Female, 65       | Sepsis | Favorable   | Australia | Geng et al. |
| Pulmonary edema | Female, 73       | Brightening episode | Favorable   | Northern Ireland | Daly et al. |
| Pulmonary edema | Female, 59       | Motor-vehicle collision | Favorable   | United States | Ritchie et al.  |
| Pneumorrhax     | Female, 64       | COPD | Favorable   | United States | Kumar et al.  |
| Pulmonary hypertension | Female, 69 | Initiation of intravenous treprostinil | Favorable   | United States | Cork et al. |
| Pulmonary hypertension | Female, 81 | Right ventricular involvement | Favorable   | Italy | Citro et al.  |
| Smoking and “Venus” | Male, 81 | Adolescent sexual intercourse | Favorable   | Italy | Brunetti et al. |

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

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. Misuma 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 cardiogenic 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 “pills 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.

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