NONCARDIAC ESOPHAGEAL CHEST PAIN - A COMPREHENSIVE REVIEW

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Abstract

Background and aim. *Noncardiac chest pain (NCCP) is a medical condition described as acute, recurrent, or chronic chest pain, that is difficult to distinguish from ischemic heart pain, when the cardiac source has been excluded. Noncardiac chest pain represents a challenging clinical situation in gastroenterology practice, requiring sometimes a high amount of clinical investigation for a specific diagnostic. In some cases, the etiology is represented by esophageal diseases. This review aims to present the updated knowledge of the esophageal origin of NCCP.*

Methods*. A search was performed in the main databases containing medical publications. The following search terms were used: noncardiac chest pain, esophageal chest pain (ECP), pathophysiology, noncardiac chest pain etiology, gastroesophageal reflux disease (GERD), motility esophagus disorders, functional chest pain. Observational studies were included. Studies that described only cardiac chest pain were excluded.*

Results*. Noncardiac chest pain requires precise recognition of signs, symptoms and diagnostic testing in clinical practice. Due to financial constraints on subsequent care, an accurate algorithm based on clinical noncardiac chest pain guidelines should be followed. Esophageal chest pain represents a challenging diagnosis.*

Conclusions*. Noncardiac chest pain is a prevalent and alarming symptom. Esophageal chest pain etiology should be considered once a cardiac source has been excluded.*

Keywords*: Noncardiac chest pain, esophageal chest pain, gastroesophageal reflux disease (GERD), esophageal motility, functional chest pain.*

Rezumat

Introducere și scop. *Durerea toracică noncardică este o afecțiune medicală descrisă ca durere toracică acută, recurentă sau cronică, care este dificil de distins de durerea cardiacă ischemică, atunci când se exclude o cauză cardiacă. Durerea toracică noncardică reprezintă o situație clinică dificilă în practica gastroenterologiei, necesitând uneori numeroase investigații pentru un diagnostic specific. În unele cazuri, etiologia este reprezentată de boli esofagiene.*



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Această lucrare își propune să prezinte informații actualizate despre durerea toracică noncardică de origine esofagiană.

Metodă. *S-a efectuat o căutare în principalele baze de date care conţin publicaţii medicale, fiind utilizați următorii termeni: durere toracică noncardiacă, durere toracică esofagiană, fiziopatologie, etiologia durerii toracice noncardiace, boală de reflux gastroesofagian, tulburări de motilitate esofagiană, durere toracică funcțională. Au fost incluse studii observaționale și au fost excluse studiile care au descris doar durerea toracică cardiacă.*

Rezultate. *Durerea toracică noncardică necesită cunoașterea precisă a semnelor, simptomelor și testelor de diagnostic în practica clinică. Din cauza constrângerilor financiare privind îngrijirea ulterioară, ar trebui urmat un algoritm precis, bazat pe ghidurile clinice pentru durere toracică noncardiacă. Durerea toracică esofagiană reprezintă un diagnostic dificil.*

Concluzii. *Durerea toracică noncardică este un simptom răspândit și alarmant. Etiologia durerii toracice esofagiene trebuie luată în considerare odată ce o sursă cardiacă a fost exclusă.*

Cuvinte cheie: *durere toracică noncardiacă, durere toracice esofagiană, boală de reflux gastroesofagian (GERD), motilitate esofagiană, durere toracică funcțională.*

Introduction

Chest pain represents a common and concerning symptom in clinical practice. Patients who present with chest pain should almost always suspected of acute coronary syndrome (ACS), which is a life threating health care issue. In practice, 20% of the patients who present with chest pain are diagnosed with ACS[1].

Therefore, the majority of the patients who presents with chest pain, 80% of them, are diagnosed with noncardiac chest pain and require noncardiac evaluation and treatment.

It has been proved that patients with NCCP depend on a similar number of doctor appointments as patients with cardiac chest pain[2]. This review aims to emphasize the importance of a correct clinical noncardiac chest pain diagnoses.

Literature has been studied in main databases of medical publications using the following search terms: noncardiac chest pain, esophageal chest pain, gastroesophageal reflux disease (GERD), motility disorders, functional chest pain. Data on pathophy-

siology, etiology, prevalence and classification of noncardiac chest pain were collected and presented.

Definition

NCCP is defined as angina-like pain which has no evidence of coronary etiology. Long time morbidity and mortality of these patients has been considered to be equivalent to long time morbidity and mortality of patients with cardiac chest pain, but recent studies that included longer time follow-up periods demonstrated that patients with NCCP show double elevation in the relative risk of adverse cardiac events over 5-26 years[3].

The incidence rate of a new diagnoses of chest pain was 15.5 per 1000 persons among primary care consultation in UK and elevated with age, especially in men. In this study were included 13740 cases with a first undefined chest pain episode. A patient with a prior diagnoses of coronary heart disease (OR: 7.1; 95% CI: 6.1–8.2) and gastroesophageal reflux disease (OR: 2.0; 95% CI: 1.7-2.3) has a higher risk of a new clinical chest pain suspicion. Also patients with prior diagnosis of heart failure, dyspepsia, hiatus hernia, chronic obstructive pulmonary disease (COPD), sleep disorders, asthma or musculoskeletal conditions have an increased likelihood of presenting with a new unspecified chest pain episode. Patients with a new diagnosis of chest pain were correlated with an increased risk of death in the next years[4].

According to a national study of the prevalence of life-threatening diagnoses in patients with chest pain in which were analyzed 10907 patient records with a prior symptom of chest pain. 75 patients aged 18-44 representing 1.7% and 56 patients aged 45-64 representing 1.5% were diagnosed with esophageal disorders[5]. The cardiac and noncardiac etiology of chest pain is presented in table 1.

Regarding causes of noncardiac chest pain, GERD represents an important one. Acid reflux in the esophagus and mucosal hypersensitivity are mechanisms of GERD. GERD presents with heartburn and acid regurgitation. Dietary changes are recommended along with pharmacological treatment with proton pump inhibitor (PPI) or H2 blockers or dispositives. A dramatic condition with NCCP is the esophageal rupture, manifested with forceful vomiting, and subcutaneous emphysema. Surgical intervention and supportive care are indicated. Esophageal spasms presents with spastic pain and dysphagia and increased amplitude on high-resolution esophageal manometry. It is treated with calcium channel blocker, nitrates and surgery[6].

Pulmonary etiology of NCCP manifests with activation of the visceral pleura, hyperinflation of the lungs which leads to pleura extension and activation of pleura receptors, resulting chest pain[6]. Obstructive airway disease manifests with shortness of breath, productive cough and a history of smoking[7].

Musculoskeletal etiology consists of costochondritis which manifests with reproducible chest pain due to increased inflammation of costosternal or costochondral joints. Infectious diseases represent another etiology which manifests with pneumonia with decreased white blood cell, productive cough, febrile state and increased neutrophil infiltration[6].

Prevalence data

The data found in the medical literature suggest that esophageal chest pain is common, affects substantially the quality of life of these patients and burdens health care system in terms of costs. The prevalence



estimated of noncardiac chest pain in clinical background is 14-33%[6].

According to a meta-analysis by Ford et al, out of 18 articles evaluated, 16 reported prevalence of noncardiac chest pain in 14 separate populations consisting of 24849 patients, prevalence of non-cardiac chest pain in all studies was 13%, higher in Australian studies and with no difference in male versus female rates (OR 0.99; 95% CI 0.82-1.20). Prevalence was higher in subjects who reported gastroesophageal reflux disease (OR 4.71; 95% CI 3.32-6.70). Prevalence was also higher related to frequency of GERD symptoms. Further studies are needed for a more accurate data on the subject[8].

Diagnosis of esophageal chest pain

Esophageal chest pain is frequently attributed to GERD due to activation of esophageal chemoreceptors. DeMeester and colleagues demonstrated that 46% of patients with noncardiac chest pain had acid reflux during pH studies[9].

In another study patients who presented esophageal chest pain presented pH positive symptom indicator in 50%[10]. Another study showed that GERD may appear in 30% to 60% of patients with esophageal chest pain(11). Nonacid reflux may also cause chest pain, but further studies are needed to demonstrate the association between nonacid reflux and esophageal chest pain[12]. Other esophagitis can cause chest pain, such as caustic, infectious, eosinophilic, drug-induces esophagitis. Eosinophilic esophagitis is defined by permanent esophageal eosinophilia, in subjects with symptoms such as feeding disorders in 2 years old, vomiting in 8 years old, abdominal pain, dysphagia, food impaction in adolescents and adults. Studies show that most adults present with dysphagia, food impaction, heartburn and chest pain[13].

Esophageal dysmotility disorders include diffuse esophageal spasm, nutcracker esophagus, achalasia, scleroderma and nonspecific motility disorders. In one study, even though 32% had dysmotility, none reported pain[10]. In this area, studies show different results: a study of 10 patients who had 24-hour endoluminal ultrasonography found sustained contractions during episodes of chest pain[14]. Nevertheless, this activity appeared only in a small group of patients and only during some of the pain episodes[12]. High resolution esophageal manometry represents the gold standard in diagnosing esophageal chest pain caused by motility changes.

Esophageal hypersensitivity is considered the central mechanism of esophageal chest pain[15]. In one study, 83% of ECP patients experienced pain at pressure distention less than 50 cm H_2O[16]. In addition, 80% of ECP affirmed that their familiar chest pain was reproduced during the test. In another study,

Cardiac chest pain	Non-cardiac chest pain
Acute miocardial infarction	Pulmonary origin
Unstable angina	Musculoskeletal
Stable angina	Mediastinal
Cocaine-induced vasospasm	Digestive (esophagus) origin
Nocturnal angina	Herpes zoster
Decubitus angina	Postherpetic neuralgia
Pericarditis	Necrotizing fasciitis
Chronic refractory angina	Panic attacks
Atypical angina	Anxious state
Mitral valve prolapse	Somatization
Aortic stenosis	
Congenital cardiac abnormalities	
Cardiac tamponade	

Table 1. *Cardiac and noncardiac etiology of chest pain*

Chicago version 3.0	Chicago version 4.0
Major motility disorders 1. Achalasia 2. EGJOO Major disorders of peristaltism 1. Distal esophageal spasm 2. Jackhammer esophagus 3. Absent contractility Minor disorders of peristalsis 1. Fragmented peristalsis 2. Ineffective motility	Disorders of EGJ outflow 1. Achalasia 2. EGJOO Disorders of peristalsis 1. Absent contractility 2. Distal esophageal spasm 3. Hypercontractile esophagus 4. Ineffective esophageal motility

Table 2. *Chicago 4.0 Classification of esophageal motility disorders*



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1. Retrosternal chest pain or discomfort, cardiac causes should be ruled out
2. Absence of associated esophageal symptoms, such as heartburn and dysphagia
3. Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis is the cause of the symptom
4. Absence of major esophageal motor disorders, achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis.

Table 3. *Rome IV criteria for functional chest pain*

esophageal hypersensitivity was present in 90% of patients with nutcracker esophagus, transmitted that sensory dysfunction causes chest pain in hypercontractile esophagus[12,17].

Esophageal cancer represents a disease whereby malignant cancer cells arrise from the mucosa[18]. The main common forms of esophageal cancer are squamous cell carcinoma and adenocarcinoma. It presents clinically with difficult or painful swallowing, first for solid and then for fluids, weight loss, nausea, vomiting, loss of appetite, chest pain and hoarseness[19].

Chicago Classification version 4.0 represents the updated classification for esophageal motility disorders using high-resolution manometry, as seen in table 2[20]. Fifty-two international experts divided into seven working group worked on this classification[21].

The updated version contains a more meticulous and extensive high-resolution manometry protocol using supine and upright test position, provocative testing, refined definition of esophagogastric junction (EGJ), outflow obstruction (EGJOO), more rigorous diagnostic criteria for ineffective esophageal motility and description of baseline esophagogastric junction metrics. The diagnosis of fragmented peristalsis is no longer part of Chicago 4.0. All the minor disorders of peristalsis are included now in the group of Ineffective esophageal motility [21].

Another major change in Chicago version 4.0 is the importance of symptoms, for a clinically relevant conclusive diagnosis. A clinically relevant conclusive diagnosis requires both

clinically relevant symptoms and manometric diagnosis[21].

According to the Lyon Consensus, the point of the GERD consensus was to discover modern indications for esophageal testing in GERD and to determine clinical diagnosis criteria of GERD. The clinical history, questionnaire data and reaction to antisecretory therapy are inadequate to make a relevant diagnosis of GERD, these are used to indicate further examination[22].

High grade erosive esophagitis (Los Angeles grades C and D), long-segment Barrett`s mucosa, peptic strictures on endoscopy, distal esophageal acid exposure time (AET) >6% on ambulatory pH or pH-impedance monitoring represent precise confirmation of GERD. A negative endoscopy does not eliminate GERD, but together with distal AET<4% and <40 reflux episodes on pH-impedance contradict a positive GERD diagnosis[23].

When endoscopy, pH or pH impedance monitoring are unconvincing, data from biopsy findings like histopathology scores, dilated intercellular spaces or motor evaluation (hypotensive lower esophageal sphincter, hiatus hernia and esophageal body hypomotility on high resolution manometry) and novel impedance metrics (baseline impedance, post reflux swallow-induced peristaltic wave index) can conduct to a GERD diagnosis[24]. Novel parameters are used as adjunctive parameters for GERD diagnosis: mean nocturnal baseline impedance (MNBI) (<2200 Ohm) and PSPWI post reflux swallow-induced peristaltic wave index (PSWI) meaning proportion of reflux episodes on pH-impedance monitoring followed by a post swallow peristaltic wave (PSPW)[25]. The PSPW index reflects the integrity of primary peristalsis stimulated by reflux episodes. Measurement of MNBI is done during sleep as average from three 10 minutes periods spaced an hour apart However, these investigations cannot provide a certain GERD diagnosis, an evaluation of anatomy, motor function, reflux burden and symptomatic phenotype will conduct management[26].

According to Rome IV functional chest pain must include all of the following criteria, fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis with a frequency of at least once a week (Table 3)[27].

Finally, Rome IV NCCP algorithm indicates that in front of a patient with chest pain of suspected esophageal origin if the clinical history and physical examination is suggestive of non-esophageal etiology the patient should be evaluated and treated accordingly[28]. If not, the risk of cardiac etiology should be evaluated with a cardiac evaluation and treated accordingly[29]. If the chest pain responds to PPI trial, GERD is presumed, and PPI are titrated for the treatment. If the upper endoscopy with biopsy ruled out eosinophilic esophagitis and there are any other abnormality identified, reflux testing with manometry should be performed. If there is abnormal esophageal acid exposure, nonerosive reflux disease is diagnosticated. If there are abnormal manometry findings a major motor disorder is present. If not, functional chest pain is present[30]. The absence of an organized diagnostic algorithm results in a supplementary burden on health care system.

Conclusions

Cardiac chest pain represents one of the most significant challenges for practitioners. Esophageal chest pain represents a significant chapter of noncardiac chest pain category, which needs to be recognized and managed according to present guidelines in gastro-enterology daily practice.



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