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BRIEF ARTICLE

Exertional esophageal pH-metry and manometry in recurrent chest pain

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Abstract

AIM: To investigate the diagnostic efficacy of 24-h and exertional esophageal pH-metry and manometry in patients with recurrent chest pain.

METHODS: The study included 111 patients (54% male) with recurrent angina-like chest pain, non-responsive to therapy with proton pump inhibitors. Sixty-five (59%) had non-obstructive lesions in coronary artery angiography, and in 46 (41%) significant coronary artery narrowing was found. In all patients, 24-h esophageal pH-metry and manometry, and treadmill stress tests with simultaneous esophageal pH-metry and manometry monitoring were performed. During a 24-h examination the percentage of spontaneous chest pain (sCP) episodes associated with acid reflux or dysmotility (symptom index, SI) was calculated. Patients with SI > 50% for acid gastroesophageal reflux (GER) were classified as having GER-related sCP. The remaining symptomatic individuals were determined as having non-GER-related sCP. During the stress test, the occurrence of chest pain, episodes of esophageal acidification (pH < 4 for 10 s) and esophageal spasm with more than 55% of simultaneous contractions (exercise-provoked esophageal spasm or EPES) were noted.

RESULTS: Sixty-eight (61%) individuals reported sCP during 24-h esophageal function monitoring. Eleven of these (16%) were classified as having GER-related sCP and 53/68 (84%) as having non-GER-related sCP. The exercise-provoked chest pain during a stress test occurred in 13/111 (12%) subjects. In order to compare the clinical usefulness of 24-h esophageal function monitoring and its examination limited only to the treadmill stress test, the standard parameters of diagnostic test evaluation were determined. The occurrence of GER-related or non-GER-related sCP was assumed as a "gold standard". Afterwards, accuracy, sensitivity and specificity were calculated. These parameters expressed a prediction of GER-related or non-GER-related sCP occurrence by the presence of chest pain, esophageal acidification and EPES. Accuracy, sensitivity and specificity of chest pain during the stress test predicting any sCP occurrence were 28%, 35% and 80%, respectively, predicting GER-related sCP were 42%, 0% and 83%, respectively, and predicting non-GER-related sCP were 57%, 36% and 83%, respectively. Similar values were obtained for exercise-related acidification with pH < 4 longer than 10 s in the prediction of GER-related sCP (44%, 36% and 92%, respectively) and EPES in relation to non-GER-related sCP (48%, 23% and 84%, respectively).

CONCLUSION: The presence of chest pain, esophageal acidification and EPES had greater than 80% specificity to exclude the GER-related and non-GER-related causes of recurrent chest pain.

Key words: Chest pain; Diagnosis; Esophageal manom-

etry; Esophageal pH-metry; Treadmill test

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INTRODUCTION

Recurrent, effort-provoked chest pain is the most common among cardiac and esophageal symptoms. It is also one of the greatest problems in contemporary health care because of its prevalence, adverse effects on quality of life, morbidity, and the utilization of health care resources[1,2]. The other problem is the frequent overlapping of causes of chest pain[3]. The presence of gastroesophageal reflux (GER)-related chest pain was confirmed in about 60% of patients with normal coronary angiography[4] and in 35% of patients with coronary artery disease (CAD)[5]. On the other hand, patients with GER presented with many co-morbidities, originating both from cardiac and noncardiac sources, which may cause chest pain[6]. For this reason, in the diagnostic procedures of chest pain, both in patients with and without significant coronary artery narrowing, it is very important to evaluate the temporal relationship between symptoms and electrocardiographic signs of myocardial ischemia and/or the occurrence of esophageal abnormalities. It has been proven that analysis of the symptom association probability (SAP), symptom index (SI) or symptom sensitivity index reproducibly increases the yield of 24-h esophageal pH-metry, manometry and impedance examination[7,8]. As a result, some provocative tests inducing symptoms, could probably make these diagnostic procedures more efficient. It was reported that esophageal testing during exercise[9-16], dynamic position changing[17] and bending[18] made the 24-h esophageal pH-metry more informative and more efficient in the detection of significant GER. Exercise can provoke symptoms and abnormalities originating both from the heart and the esophagus[11,16]. Therefore, it was made a hypothesis that the simultaneous monitoring of clinical, electrocardiographic and hemodynamic parameters, as well as esophageal pH and pressure during the treadmill stress test, might also provide a more accurate means to evaluate the temporal interrelation between chest pain occurrence and myocardial and esophageal disturbances than separate tests[19]. Such a procedure might be useful, especially in patients non-responsive to empirical therapy with proton pump inhibitors (PPI)[7], both with and without significant coronary artery narrowing in coronary artery angiography, because of the above mentioned overlap in the causes of chest pain[5,20]. In addition it may allow the possibility of diagnosing myocardial ischemia in patients with non-obstructive coronary artery lesions due to microvascular angina[2] or the ischemic effect of the cardio-esophageal reflex[21]. The cardio-esophageal reflex is a vagal, visceral neural reflex, which may be activated by changes in intra-esophageal pH, pressure or temperature. Its stimulation may lead to a decrease in myocardial perfusion, proven in invasive[21,22] and non-invasive examinations[23], as well as to the occurrence of electrocardiographic signs of myocardial ischemia[5,24] or arrhythmia[19,25-29]. The mentioned effects were confirmed in about 56% of subjects with a normal coronarography[21] and in some subjects with significant coronary artery narrowing[24]. On the other hand, products of anaerobic myocardial metabolism, especially bradykinin[30], or invasive procedures on coronary arteries[22] *via* neural pathways may lead to esophageal dysmotility and reflux. These relationships connect ischemic heart disease and esophageal disorders in a vicious circle.

It is known that the activation of vagal reflexes may change the autonomic nervous system balance. In this way, abnormalities in intraesophageal pH[31,32] and pressure may also lead to a decrease in pain threshold and hypersensitivity[33]. This may explain why, in many studies, time-dependence between GER, esophageal dysmotility and chest pain episodes was relatively small and amounted to 22%-65%, and why many of the patients with noncardiac chest pain remained symptomatic in spite of detailed diagnosis and appropriate treatment[4]. These complicated interrelations assumed the planning of further studies to evaluate the new diagnostic tools in patients with recurrent chest pain of suspected noncardiac origin, as well as to determine more easily, and in a shorter time, the causal associations between esophageal disorders and patients' symptoms.

The aim of this study was to estimate the diagnostic efficacy of esophageal pH-metry and manometry monitoring during a treadmill stress test in comparison to 24-h esophageal pH-metry and manometry in patients with recurrent angina-like chest pain. In other words, this study addresses whether it is possible to replace 24-h esophageal function monitoring by an examination limited only to a treadmill stress test.

MATERIALS AND METHODS

One hundred and twenty-nine consecutive patients diagnosed with recurrent angina-like chest pain of suspected noncardiac origin were investigated. The symptoms were suspected of being of noncardiac origin by the leading doctor, independently of the researcher, who referred his patients for gastroenterological diagnosis after a cardiac work-up because of recurrent symptoms resistant to standard treatment oriented to coronary reserve improvement and empirical therapy with PPI. The pre-referral cardiac diagnostics procedures covered history, physical examination, electrocardiogram (ECG), treadmill stress test, and coronary artery angiography (Table 1). An extracardiac source of chest pain was suspected because none of the referred patients presented with an association between chest pain and ischemic changes during a treadmill stress

Table 1 Demographic and clinical data of investigated patients with a comparison of subjects without and with significant (> 50%) coronary artery narrowing *n* (%)

Parameter	Significant coronary artery narrowing	
	No (*n* = 65)	Yes (*n* = 46)
Males/females	29/36 (45/55)	31/15 (67/33)
Age (yr)	55.0 ± 8.8	55.0 ± 8.8
BMI (kg/m^2)	28.7 ± 4.2	27.8 ± 3.9
WHR	0.94 ± 0.9	0.93 ± 0.07
Smoking	11 (17)	10 (21)
History of PCI	0	21 (46)[a]
History of CABG	0	9 (19)[a]
History of myocardial infarction	0	18 (40)
Hypertension	24 (39)	24 (52)
Systolic blood pressure (mmHg)	122.8 ± 17.7	123.4 ± 17.4
Diastolic blood pressure (mmHg)	82.0 ± 11.2	81.1 ± 9.3
Diabetes mellitus	4 (5)	7 (13)
Total cholesterol (mg/dL)	195.7 ± 28.1	218.9 ± 48.3[a]
LDL cholesterol (mg/dL)	122.7 ± 25.9	136.1 ± 39.6
HDL cholesterol (mg/dL)	52.1 ± 11.9	48.5 ± 12.9
Triglycerides (mg/dL)	100.1 ± 33.0	166.1 ± 84.5[a]
Blood glucose (mg/dL)	100.2 ± 15.8	95.0 ± 17.7
Stress test duration (s)	455 ± 172	549 ± 191[a]
ST interval depression > 1 mm without chest pain during treadmill (silent ischemia)	28 (43)	17 (37)
Chest pain without ST interval depression during stress test	9 (14)	4 (9)
GER-related chest pain	7 (11)	4 (9)
Non-GER-related chest pain	35 (54)	22 (48)
Erosive esophagitis in endoscopy	16 (25)	17 (37)
Pathological GER	19 (29)	16 (35)
DES	13 (20)	10 (22)
epGER	12 (18)	4 (9)
epDES	14 (22)	9 (20)

Data presented as *n* (%) or mean ± SD. [a]$P < 0.05$ in an unpaired Student *t*-test or Fisher exact test. BMI: Body mass index; WHR: Waist/hip ratio; LDL: Low density lipoprotein; HDL: High density lipoprotein; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; GER: Gastroesophageal reflux (> 4.5% time of esophageal monitoring with pH < 4); DES: Diffuse esophageal spasm, defined as esophageal motility abnormality with more than 30% of simultaneous contractions; epGER; Exercise-provoked GER, defined as a decrease in esophageal pH during a stress test for more than 10 s.

test. However, in spite of the results of the pre-referral cardiological diagnostic procedures, angina-like chest pain connected with electrocardiographic signs of myocardial ischemia was observed during the treadmill stress test conducted in the clinic in 18 subjects with significant coronary artery narrowing in angiography. These patients were excluded from the analysis because it would be impossible to distinguish between cardiac and extracardiac sources of chest pain, especially in patients with significant coronary artery disease. Finally, 111 consecutive subjects were included in the analysis, and fulfilled the following inclusion criteria: (1) age between 40 and 70 years; (2) prior coronary angiography performance not earlier than 3 mo before gastroenterological work-up; (3) angina-like chest pain to a degree of class Ⅱ in accordance with the Canadian Cardiovascular Society; such a pattern of chest pain was defined as precordial symptoms induced by exercise of less than, for example, marching for a distance under 200 m, and receding after rest or taking nitroglycerine; the occurrence of such defined chest pain during a treadmill stress test cannot be accompanied by signs of myocardial ischemia in the ECG; and (4) persistent symptoms despite adequate anti-anginal treatment (in patients with significant coronary artery lesions) and at least 1 mo-long therapy with a double dose of omeprazole, both in patients with and without significant coronary artery narrowing. Such a course of symptoms justified a suspicion of an extracardiac cause of chest pain, resistant to empirical therapy with PPI, and provided reasons for gastroenterological diagnostics to be undertaken. The exclusion criteria were: the presence of changes in the resting ECG, which made it impossible to estimate signs of myocardial ischemia (e.g. left bundle branch block or pre-excitation syndrome). All patients were asked not to take histamine receptor type 2 antagonists (e.g. ranitidine and famotidine), PPI or prokinetics (metoclopramide, cisapride, trimebutine and mebeverine).

Finally, the study group consisted of 46 (40%) patients with significant coronary artery changes, more than 50% of them with narrowing of the arteries, although not suitable for revascularization, and 65 (60%) subjects showing a normal coronary arteriography or no obstructive coronary lesions. Clinical and demographic data of the studied patients were divided according to the presence of significant narrowing of the coronary vessels (Table 1). Neither group differed in relation to the majority of these (Table 1). During the investigation, patients continued taking the stable doses of previously prescribed drugs (i.e. for CAD, hypertension and diabetes).

In all subjects, the medical history, physical examination, panendoscopy with gastric and esophageal biopsy, 24-h esophageal pH-metry and manometry were performed "off-therapy". An investigation of ambulatory esophageal function was carried out using a multi-use antimony probe (Synetics Medical AB, Sweden), a manometry catheter (Synectics, Medtronic) with 3 pressure sensors separated by 5 cm, and a Synectics micro-Digitrapper. An esophageal pH-metric sensor, after calibration to pH 7 and 1, using nasal and esophageal intubation, was positioned 5 cm above a monometrically-determined lower esophageal sphincter (LES). Pressure transducers were located through the other nostril at 3, 8 and 13 cm above the LES. During esophageal pH and pressure monitoring, all patients recorded occurring symptoms. None of the patients reported disturbances in nasal breathing. Every chest pain appearing during 24-h esophageal function monitoring was recorded by the micro-Digitrapper and labelled spontaneous chest pain (sCP).

The following day, when patients had become accustomed to the presence of the pH-metric and manometric probes in their nostrils, a treadmill stress test on a running track was carried out at approximately 7 am during continuous esophageal pH-metry and manometry

monitoring. The exercise test was performed using a device manufactured by Schiller, Switzerland, according to the Bruce protocol (the speed and gradient of the running track were increased every 3 min to 2.7, 4, 5.5 and 6.8 km/h, and by 10°, 12°, 14° and 16°). The start and finish of the exercise during the treadmill stress test as well as exercise-provoked angina-like chest pain (epCP) episodes were marked on the micro-Digitrapper.

The obtained data were downloaded to a personal computer and analyzed using GASTROSOFT software. Standard pH-metric and manometric parameters were calculated[34]. The GASTROSOFT software also analyzed the relationships between chest pain and the type of esophageal abnormality (a decrease in esophageal pH, changes in esophageal pressure or peristaltic wave coordination). This analysis concerned a period of 2 min prior to and during chest pain episodes. Patients were classified as having "GER-related" chest pain when the SI, defined as a percentage of sCP episodes associated with acid reflux during 24-h esophageal pH-metry, was $\geqslant$ 50%. Patients were classified as having "non-GER-related" chest pain if the percentage of sCP episodes during 24-h esophageal pH-metry and manometry associated with esophageal dysmotility was $\geqslant$ 50% and the individual did not fulfill GER-related chest pain criteria. Esophageal dysmotility was classified following esophageal manometry parameters presented during chest pain or in periods of 2 min prior to its appearance, non-peristaltic contractions, or contractions with amplitude or duration exceeding 95% of their daily average value.

Apart from types of sCP and esophageal abnormalities appearing within 24-h esophageal examination, additional symptoms and esophageal pH-metric and manometric abnormalities occurring during the treadmill stress test were determined. Angina-like chest pain (retrosternal pressing) appearing during the treadmill stress test was termed exercise-provoked chest pain (epCP). Gastroesophageal acid reflux provoked by exercise (epGER) was defined as a decrease in esophageal pH to below 4 for more than 10 s during the exercise stress test. Exercise-provoked esophageal spasm (EPES) was diagnosed when the percentage of simultaneous contractions during the treadmill stress test exceeded 55%. Simultaneous contractions, according to gastrosoft software settings, were defined as a sequence of contractions with less than 0.25 s delay between adjacent transducers separated by 5 cm (a propagation speed higher than 20 cm/s). The value of the cut-off at the level of 55% originated from the work by Stein *et al*[35], who proposed such diagnostic criteria for diffuse esophageal spasm in 24-h manometry.

Ethics

The study protocol was approved by the local Bioethics Committee of Nicolaus Copernicus University in Toruń and the Collegium Medicum in Bydgoszcz, Poland. All subjects gave their informed consent prior to the start of enrolment procedures. All procedures have been conducted in compliance with the Declaration of Helsinki.

Table 2 Parameters for the clinical usefulness of exercise-provoked chest pain, exercise-provoked gastroesophageal reflux, and exercise-provoked esophageal spasm in the diagnosis of gastroesophageal reflux-related and non-gastroesophageal reflux-related spontaneous chest pain based on 24-h esophageal function examination (n = 111) (%)

Parameter	epCP for both sCP	epCP for GER-related sCP	epCP for non-GER-related sCP	epGER for GER-related sCP	EPES for non-GER-related sCP
Accuracy	28	42	57	44	48
Sensitivity	35	0	36	36	23
Specificity	80	83	83	92	84
PPV	64	0	64	44	59
NPV	55	89	61	89	53
LR+	1.75	0	2.1	4.5	1.4
LR-	0.81	1.2	0.77	0.7	0.92

epCP: Exercise-provoked chest pain; sCP: Spontaneous chest pain; EPES: Exercise-provoked esophageal spasm; GER: Gastroesophageal reflux; PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio.

Statistical analysis

Statistical analysis was conducted using a licensed version of statistical software STATISTICA PL 8.0 for Windows. The results were mainly presented as the mean ± SD or n (%). The normal distribution of variables was estimated using the Kolmogorov-Smirnov test. The comparison of demographic and clinical data between patients with and without significant coronary artery narrowing (Table 1) was made using an unpaired Student t-test (for quantitative variables) and the Fisher exact test for qualitative variables. In addition, the standard parameters of diagnostic test usefulness according to evidence-based medicine (EBM), e.g. accuracy, sensitivity, specificity, positive and negative predictive values, as well as the positive and negative likelihood ratios, were calculated. The diagnosis of GER-related and non-GER-related chest pain acted as a "gold standard" (reference point) for this analysis. According to such assumptions, the parameters of diagnostic test usefulness expressed the relationships between the occurrence of exercise-related disturbances (epCP, epGER, EPES) and diagnoses of GER-related and non-GER-related sCP in 24-h esophageal pH-metry and manometry. This means that they expressed the ability of exercise-related esophageal abnormalities to predict the presence of GER-related or non-GER-related sCP. Accuracy was defined as the proportion of subjects with and without spontaneous chest pain and the presence or lack of evaluated esophageal function disorder (e.g. EPES). This represented the ratio of patients with true positive and true negative results to the total number of subjects. Sensitivity, i.e. the percentage of true positive results, was defined as the proportion of subjects with a respective kind of sCP in 24-h esophageal examination (GER-related or non-GER-related) and the simultaneous presence of epCP, epGER or EPES during the treadmill stress test (Table 2). Specificity, i.e. the percentage of true negative

results, was defined as the proportion of asymptomatic subjects during 24-h esophageal pH-metry and manometry in whom evaluated exercise-related disorders (e.g. epCP, epGER and EPES) did not appear during the treadmill stress test (e.g. epGER and EPES) (Table 2). The positive predictive value (PPV) was defined as the percentage of subjects with the presence of an evaluated parameter (e.g. EPES) having chest pain during 24-h esophageal pH-metry and manometry (true positive/true + false positives). The negative predictive value (NPV) was defined as the percentage of patients without an evaluated parameter (e.g. epCP, epGER or EPES) in whom chest pain during 24-h esophageal pH-metry and manometry did not appear (true negative/true + false negatives). The positive diagnostic likelihood ratio (LR+) was defined as an odds ratio of likelihood that a patient with chest pain during 24-h esophageal pH-metry and manometry would have an evaluated disorder to the probability that an individual without chest pain would have this esophageal disturbance [LR+ = sensitivity/(1-specificity)]. However, a negative likelihood ratio (LR-) represented the odds ratio that the lack of an evaluated esophageal disorder (e.g. EPES) would be observed in subjects with chest pain during 24-h esophageal function monitoring compared with whether the same results would be observed in individuals with spontaneous chest pain; LR- = (1-sensitivity)/specificity.

RESULTS

Patients with and without significant coronary artery disease had a similar prevalence of estimated esophageal abnormalities (Table 1). During 24-h esophageal pH and pressure monitoring, 68/111 (61%) individuals were symptomatic and presented with sCP. Among them, 11/68 (16%) experienced GER-related sCP and in 57/68 (84%) non-GER-related sCP was diagnosed. These frequencies in patients both with and without significant coronary artery narrowing were similar.

In only 13/111 (12%), epCP not connected with signs of myocardial ischemia was observed and appeared significantly less frequently than sCP during 24-h esophageal pH-metry and manometry ($P = 0.0001$). The prevalence of epCP was not significantly greater in patients without CAD (Table 1). Chest pain during the stress test occurred in 6 subjects who did not show symptoms during 24-h pH-metry and manometry. This corresponded with 5% of all subjects and 14% (6/43) of individuals who did not report sCP during daily monitoring.

The monitoring of intraesophageal pH and pressure during the treadmill stress test revealed some exercise-provoked esophageal abnormalities, i.e. intraesophageal acidification, labeled epGER, in 16/111 (14%) of all subjects and EPES in 23/111 (21%) (Table 1). Of these patients, epGER was diagnosed in 4 (4%) and EPES in 13 (12%), who had no esophageal abnormalities (i.e. erosive esophagitis, pathological gastroesophageal acid reflux or diffuse esophageal spasm) in panendoscopy and in 24-h esophageal pH-metry and manometry. However, these esophageal disorders were not significantly related to chest pain presence during the treadmill stress test. Symptomatic epCP was noted in only 14% of epGER episodes ($P > 0.05$) and in 30% of EPES ($P > 0.05$).

In the next part of the analysis, the clinical usefulness of a short protocol of esophageal examination, limited only to treadmill stress test duration, was estimated and compared to the diagnostic efficacy of 24-h pH-metry and manometry, expressed by the diagnosis of GER-related or non-GER-related (dysmotility-related) sCP. This acted as the "gold standard". The occurrence of epCP, epGER and EPES during the stress test had only acceptable specificity as did the NPV value in the diagnosis of GER-related or non-GER-related sCP (Table 2). A separate analysis performed in patients both with and without significant coronary artery narrowing was conducted with similar results.

DISCUSSION

This study has addressed the question of whether it is possible to replace 24-h esophageal pH-metry and manometry with a short protocol of these examinations limited only to stress test duration in the diagnosis of noncardiac chest pain originating from the esophagus. In other words, this investigation estimated exercise as a provocative test offering a greater possibility of correlating symptoms with esophageal abnormalities and excluding the potential life-threatening state connected with myocardial ischemia. The obtained results met the assumed requirements only in part.

The main finding of this study was that diagnoses of exercise-related esophageal disorders, such as epCP, epGER and EPES, had high values of specificity and NPV (Table 2). This makes them useful in excluding rather than confirming an esophageal source of recurrent angina-like chest pain, non-responsive to PPI, in patients both with and without significant coronary artery narrowing. This means in practice that 24-h pH-metry and manometry would not offer any important information concerning the cause of chest pain, if a patient, non-responsive to empirical therapy with PPI, did not present retrosternal symptoms during a treadmill stress test (e.g. conducted during a cardiologic work-up). Similar conclusions prompted the diagnosis of epGER and EPES during exertional esophageal pH and pressure monitoring during a treadmill stress test. A recognition of epGER or epCP in patients non-responsive to PPI was weak in this study (LR+ > 2 or LR- < 0.5) or uncertain (LR+ < 2 or LR- > 0.5), regarding parameters in the prediction of GER-related and non-GER-related spontaneous chest pain appearance during 24-h esophageal function monitoring.

The next observation of this study, as well as the next argument against recommending 24-h esophageal pH and pressure monitoring substitution by their examination only during a treadmill stress test, was that chest pain appeared during the stress test significantly and several times less frequently than during the 24-h investi-

gation. This did not correlate with esophageal pH-metric and manometric abnormalities. This shows that esophageal monitoring during a treadmill stress test, although providing the possibility of diagnosing epGER in an additional 4% of patients and EPES in an extra 12% of subjects, did not increase the probability diagnosis of the origin of chest pain, mainly because of the low SI value. In addition, the outcome of epGER and EPES diagnosis was still obscure.

In the available papers, I did not find any analysis using EBM parameters of diagnostic test evaluation in patients with recurrent chest pain who were non-responders to PPI. However, it was reported that esophageal testing during exercise[9-16], dynamic position changing[17] and bending[18] made 24-h esophageal pH-metry more efficient in the detection of significant GER. Bovero *et al*[10] showed that the provocation of gastroesophageal acid reflux by exercise might improve the diagnostic efficiency of esophageal pH-metry. The clinically useful provocative effect of exercise on gastroesophageal reflux has also been reported by other authors[11-18]. Furthermore, Ravi *et al*[9], investigating the effect of treadmill use on esophageal motility, found that exercise decreased the esophageal wave amplitude in patients with GERD, nutcracker esophagus and diffuse esophageal spasm (DES). Unfortunately, the authors did not discuss the outcome of exercise on the effectiveness of esophageal motility, so they could reveal DES-like exertional motility disorders such as EPES. Some authors have shown one questionable role of esophageal motility disorders in noncardiac chest pain pathogenesis[35,36], mainly because of the personally-dependent overlapping of other noncardiac chest pain pathomechanisms, such as hypersensitivity or musculoskeletal disorders[4,33]. However, Adamek *et al*[20] have confirmed the role of esophageal spasm in noncardiac chest pain pathogenesis, reporting an increase in simultaneous contractions in patients with chest pain, both with and without significant coronary artery narrowing, in comparison to asymptomatic controls. Apart from the above mentioned discrepancies, in my opinion, my results might have a clinical importance. Firstly, they provide an analysis of the classic diagnostic procedures of noncardiac chest pain both in patients with and without significant coronary artery narrowing; unfortunately, in everyday praxis, the overlapping of causes of noncardiac chest pain in therapy-resistant patients with CAD is rarely recognized[3]. Secondly, they show the importance of angina-like chest pain analysis in the diagnosis, not only of cardiac but also noncardiac sources of chest pain. It is known that chest pain appearance during a treadmill stress test increases its clinical usefulness. My investigation showed that a lack of chest pain during a typical cardiological exercise test predicted the low diagnostic importance of 24-h esophageal pH-metry and manometry. This information may shorten the diagnostic process and prevent the performance of useless examinations and resource utilization because of the implied consideration of extraesophageal chest pain causes if a stress test during a cardiological work-up did not provoke chest pain. Thirdly, the tests showed that the newly-defined esophageal motility disorder of EPES with high specificity allowed the prediction of a lack of esophageal manometry usefulness in the diagnosis of non-GER-related chest pain. The influence of EPES diagnosis on the course of chest pain over a 2.7-year long follow-up will be discussed in other work.

This study, however, has certain limitations. The first results were from a small subject sample, but this was still greater than for the majority of works concerning diagnostic and therapeutic problems in patients with suspected noncardiac chest pain[4,9,10,20,21,36-50]. Secondly, diagnostic procedures were made "off-therapy", which was inconsistent with the majority of recommendations by Fass, Hirano and Sifrim suggesting chest pain investigation "on-PPI-therapy"[36,51,52]. However, a recent study considered the necessity of returning to such ("off-therapy") an esophageal function examination[7,53-55]. Thirdly, the reference points in the analysis of respective diagnostic test usefulness were subjective and susceptible to the effect of esophageal hypersensitivity, one being between the main noncardiac chest pain pathomechanisms[4,33,36]. On the other hand, the evaluation of relationships between symptoms and esophageal abnormalities is an acceptable method to increase the diagnostic yield of esophageal 24-h examinations[8]. However, a more reliable parameter for this purpose is SAP, not SI. Fourthly, esophageal pH-metry and 24-h manometry have recently been substituted by esophageal impedance with pH-metry and high resolution manometry[56,57] but, in particular, the latter does not seem to be useful in the diagnosis of esophageal function during a treadmill stress test.

In conclusion, the occurrence of angina-like chest pain, a decrease in esophageal pH to below 4, and an increase in simultaneous contraction percentage above 55% during a treadmill stress test has acceptable specificity and NPV to exclude an origin from the esophagus, both for GER-related and non-GER-related causes of recurrent chest pain, in comparison to the results obtained during 24-h esophageal function monitoring. However, less frequent chest pain appearance during a treadmill stress test than during 24-h esophageal function monitoring limits the clinical usefulness of this provocative examination to the diagnosis of previously unrecognized myocardial ischemia and exercise-provoked esophageal disorders such as epGER or EPES.

COMMENTS

Background

This article concerns a very important and still current problem in clinical praxis, which is the diagnosis of chest pain. The diagnostic procedures are often time-consuming, and their clinical yield is useful only 20%-60% of individuals. For this reason new diagnostic protocols are still being investigated, including provocative tests.

Research frontiers

The study was performed in a relatively small number of patients and needs confirmation. However, its results may be helpful both for cardiologists and gastroenterologists, especially as it was performed in patients who were unresponsive to proton pump inhibitors therapy, the first-line tool in the diagnosis

of gastroesophageal reflux-related chest pain. The shortcoming of it was in not using a more sensitive examination which might more securely differentiate between cardiac and esophageal exercise-provoked chest pain.

Innovations and breakthroughs

This study has shown that the asymptomatic course of the treadmill stress test predicted a low yield of esophageally-oriented diagnostic procedures for chest pain. In addition, this study showed a similar prevalence of esophageal abnormalities in patients with and without coronary artery disease.

Applications

The results of this study, after confirmation with a greater number of subjects, may change the strategy of chest pain diagnosis of suspected esophageal origin. The results imply a lack of usefulness of esophageal function monitoring in patients in whom a cardiological work-up did not provoke symptoms.

Peer review

The manuscript presents some interesting and novel results, however, the numbers are small. This is an original paper, which would be an asset to the journal.

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