Relationship between gastroesophageal reflux disease and myocardial ischemia. Influence of reflux on temporary activity of autonomic nervous system

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Abstract

Purpose: Assessment of the gastroesophageal reflux disease (GERD) influence on myocardial ischemia and autonomic nervous system (ANS) activity.

Material and methods: In 50 patients with angiographically confirmed ischemic heart disease (IHD) in I–III CCS class, simultaneous 24-hour ECG and esophageal pH-metry monitoring was performed. We assessed: (1) GERD occurrence in patients with IHD, (2) influence of pathological reflux (PR) on myocardial ischemia – number and total duration of ST depression episodes in GERD and non-GERD patients, (3) temporary activity of ANS was determined according to the dynamics of spectral HRV (Heart Rate Variability) analysis components (LF, HF, VLF, LF/HF).

Results: 23 patients (46%) fullfilled the GERD criteria. Patients with GERD had significantly higher number of ST depression episodes (4.13 vs 2.85, $p = 0.013$) as well as longer total duration of ischemia (64.73 vs 35.2 min, $p = 0.034$). Spectral HRV analysis showed the significant decrease of LF/HF ratio ($p < 0.035$), which indicates the sympathovagal balance shift towards the parasympathetic system caused by PR.

Conclusions:

1. GERD is frequent condition in patients with angiographically confirmed IHD. Coexistence of GERD may predispose to the myocardial ischemia.
2. Gastroesophageal reflux may cause the shift of sympathovagal balance towards its parasympathetic component. This mechanism may induce esophago-cardiac reflex, leading to diminished myocardial perfusion.

Key words: ischemic heart disease, gastroesophageal reflux disease, activity of authonomic nervous system, spectral HRV analysis.

Abbreviations: GERD – gastroesophageal reflux disease, ANS – autonomic nervous system, IHD – ischemic heart disease, CCS – Canadian Cardiovascular Society, PR – pathological reflux, TIB – total ischemic burden, LF – low frequency, HF – high frequency, VLF – very low frequency, LH/HF – temporary activity of ANS, TP – total power, PTCA – percutaneous transluminal coronary angioplasty, CABG – coronary artery by-pass graft.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diseases of upper part of digestive tract. Symptoms of GERD may be typical (heartburn) or atypical: non-cardiac chest pain (NCCP), cough, asthma symptoms, laryngitis [1,2]. The incidence of GERD is high (30-50%) among patients with ischemic heart disease (IHD) confirmed in angiography [3-5]. Results of numerous studies show mutual influence of both conditions on each other. Nitrates and calcium channel blockers, by reduction of the lower esophageal sphincter tension and relaxation of intramural esophageal muscles, may cause the increase of acidic content regurgitation from stomach to esophagus and may diminish the esophageal clearance. On the other hand, reflux may also increase the myocardial ischemia [3-5]. In experimental model such correlation was confirmed by Chauhan et al., who showed significant reduction of flow in left anterior descendent artery after the esophagus perfusion with acid. This phenomenon was observed both in the group of patients with X syndrome and in patients with atherosclerosis of

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coronary arteries, however it was absent in patients after heart transplantation (denervated heart). These results led to the conclusion, that reduction of myocardial perfusion is caused by nervous reflex, and the phenomenon was called "linked angina" [6,7]. Existence of esophago-cardiac reflex was confirmed in Bortolotti's studies. Inflation of a balloon in esophagus had significant influence on mean RR intervals in ECG recorded before and after the esophagus irritation [8]. The aim of the present study is to assess the influence of gastroesophageal reflux on myocardial ischemia and to investigate the correlation of reflux with components of spectral frequency domain analysis of heart rate variability (HRV). The frequency domain analysis of HRV is mathematical transformation of selected ECG recordings, which enables finding compartments with similiar R-R interval time – Fast Fourier Transform (FFT). These compartments reflect the activity of autonomic nervous system.

Material and methods

The study was conducted in the group of patients with stable IHD in 2nd or 3rd functional class according to CCS (Canadian Cardiovascular Society), with inducible ischemia in non-invasive tests and significant lesions in coronary arteries confirmed in angiography. Patients with urgent indications for coronary arteries revascularization (PTCA or CABG) were excluded from further investigation. At inclusion the intensity of anginal symptoms was analyzed (II or III CCS class), symptoms of GERD were not analyzed. Only patients who did not take drugs reducing the hydrochloric acid production for at least 2 weeks were included into the study. Drug therapy of IHD remained unchanged (neither the types of drugs nor their doses) for a month before the inclusion as well as during the study. In 50 patients (M-42; F-8; mean age 55.9, 37-74) simultaneous 24-hour ECG and pH-metry monitoring was performed.

Esophageal pH-metry:

Esophageal pH was measured with antimon electrode (Syntetics, Sweden) and epidermal reference electrode (Ag/AgCl). In each case the electrode was calibrated, and placed in the esophagus, 5 cm above the manometrically localized lower esophageal sphincter. Polygram software was used to analyze pH (PW-version 2.04 Esophogram-version 2.01).

The following parameters were evaluated in esophageal pH monitoring [9]:

1. Time percentage of esophageal pH lower than 4 during 24 hours (FT – fractional time).

2. Total time of pH lower than 4 (TT pH<4 – total time)

3. A number of pathological refluxes (PR – pathological reflux – drop of esophageal pH<4 lasting more than 5 minutes).

24-hour ECG monitoring: In Holter ECG monitoring ST depression >1 mm was considered significant. ECG monitoring was performed using the Reynolds Medical Pathfinder 700. The following variables of ECG monitoring were assessed:

1. The number of ST segment depression episodes (ST dep);

2. The total time of ST segment depression during 24 hour monitoring (TIB – total ischemic burden).

Spectral HRV analysis was performed only in those patients, in whom >95% of R waves were identified as of sinus origin. After the initial analysis, selected ECG recordings underwent the computerized Fast Fourier Transform (FFT). Analysis of short-term recording was selected in order to evaluate the temporary activity of ANS. The following parameters were assessed [10]:

LF – low frequency [ms^2] range 0.5-0.05 Hz: component of sympathetic nervous system activity; HF – high frequency [ms^2] range 0.15-0.5 Hz: component of parasympathetic nervous system activity; VLF – very low frequency [ms^2] range <0.05 Hz – component expressing the activity of renin – angiotensin system and thermoregulation; LF/HF – temporary activity of ANS (sympathovagal balance); TP – total power [ms^2].

Influence of pathological refluxes (PR) on temporary activity of ANS was evaluated by assessment of dynamic changes in spectral HRV analysis parameters in 3 consecutive compartments:

1 compartment (-1): 10 min before the reflux appearance (control compartment);

2 compartment (0): first 10 minutes of reflux;

3 compartment (+1): 10 following minutes.

Spectral HRV analysis parameters were assessed and changes of the evaluated parameters were analyzed as the results of ANS activity alterations due to PR.

Protocol of the study has been approved by Bioethic Commitee of the Medical University of Bialystok.

Statistical analysis:

Statistical analysis was performed using the SPSS package, release 8.0.0 pl. The data are reported as maximum, minimum, mean and standard deviation (SD). Nonparametric Mann-Whitney U test was used when the data were not normally distributed.

The Wilcoxon Matched-Pairs Signed-Ranks test was used for pairs of dependent variables not normally distributed. A result was considered statistically significant when the P value was <0.05.

Results

Tab. 1 lists major clinical and angiographic data. In coronarography a lesion was considered significant when coronary artery lumen was narrowed by at least 70%, with accompanying symptoms of myocardial ischemia. The results of the 24-hour simultaneous Holter and esophageal pH monitoring are shown in *Tab. 2*. Patients were divided into two groups on the basis of pH-metry results:

- Group 1: GERD (-): 27 (54%) patients with FT<5%; patients not fulfilling the pH criteria for the diagnosis of the gastroesophageal reflux disease.
- Group 2: GERD (+): 23 (46%) patients with FT<5%; patients fulfilling the pH criteria for the diagnosis of the gastroesophageal reflux disease.

There were no differences in mean age, rates of hypertension, diabetes mellitus, past history of myocardial infarction and the severity of angina classified by the CCS between the groups. The severity and localization of coronary lesions, rates of anti-

Table 1. **Clinical and angiographic characteristics of the studied patients**

Study population 50 pts (100%)	N (%)
Arterial hypertension	30 (60)
Diabetes mellitus	13 (26)
Previous myocardial infarction	24 (48)
Angina class II CCS	29 (58)
Angina class III CCS	21 (42)
Beta blockers	45 (90)
Calcium channel blockers	26 (52)
Nitrates	45 (90)
Left anterior descending (LAD)	25 (50)
Circumflex coronary artery (Cx)	25 (50)
Right coronary artery (RCA)	32 (64)
1 vessel disease (1VD)	24 (48)
2 vessel disease (2VD)	20 (40)
3 vessel disease (3VD)	6 (12)

CCS – Canadian Cardiovascular Society, LAD – left anterior descendent coronary artery, Cx – circumflex coronary artery, RCA – right coronary artery, 1 VD – one vessel disease, 2 VD – two vessel disease, 3 VD – three vessel disease

Table 2. **Results of simultaneous monitoring esophageal pH and ECG in the study population**

variable	mean	SD	Minimum	Maximum
FT [%]	10.52	12.24	0.2	45,9
TT [min]	140.42	176.22	2.0	685.0
RP [n]	4.48	6.01	0	29
ST dep [n]	4.36	4.64	0	20
TIB [min]	58.05	77.79	0	452.50

FT [%]: time percentage of pH lower than 4 during 24 hours pH-metry (FT – fractional time); TT [min]: total time of pH<4; RP [n]: number of pathological refluxes; ST dep [n]: number of ST depression episodes; TIB [min]: total time of ST depression during Holter monitoring

Table 3. **Comparison of patients: GERD (-) Group and GERD (+) Group**

	GERD (–) 27 pts (54%)	**GERD (+)** 23 pts (46%)	**p**
Age	56.77 (±10.57)	53.08 (±7.65)	NS
Sex (male)	24 (88.9)	18 (78)	NS
Arterial hypertension	19 (70.4)	11 (47.8)	NS
Diabetes mellitus	2 (25.9)	6 (26.08)	NS
Previous MI	12 (44.4)	12 (52.2)	NS
II CCS	15 (55.5)	14 (60.86)	NS
III CCS	12 (44.5)	9 (39.13)	NS
LAD	16 (59.25)	9 (39.13)	NS
Cx	18 (66.7)	14 (60.86)	NS
RCA	10 (37)	15 (65)	0.09
1VD	14 (51.85)	10 (43.48)	NS
2VD	9 (33.3)	11 (47.8)	NS
3VD	4 (14.8)	2 (8.69)	NS
Beta blockers	24 (88.9)	21 (91.3)	NS
Calcium blockers	16 (59.25)	10 (43.48)	NS
Nitrates	22 (81.5)	23 (100)	NS

CCS – Canadian Cardiovascular Society, LAD – left anterior descendent coronary artery, Cx – circumflex coronary artery, RCA – right coronary artery, 1 VD – one vessel disease, 2 VD – two vessel disease, 3 VD – three vessel disease. Group 1: GERD (-) patients without gastroesophageal reflux disease, Group 2: GERD (+) patients with gastroesophageal reflux disease. (Statystical analysis: Mann – Whitney U Test and Chi^2 test)

Table 4. **The comparison of number of ST depression (ST dep [n]) and total ischemic burden TIB [min] in both, selected according to the results of esophageal pH-metry groups**

	GERD (+)	**GERD** (-)	**p**
ST dep [n]	2.85	4.13	0.013
TIB [min]	35.2	64.73	0.034

St dep – depression of ST segment, TIB – total ischemic burden (Statystical analysis: Mann – Whitney U Test)

anginal drug administration (nitrates, beta blockers, calcium antagonists) were comparable in both groups. The detailed data are shown in *Tab. 3*.

During the 24-hour esophageal pH-monitoring, a total number of 224 pathologic acidic refluxes was recorded in 42 patients (84%). In 23 (46%) patients FT≥5% was shown – these patients fulfilled the GERD criteria (GERD + group). Forty two patients (84%) had 218 ST-segment depression episodes during the 24-hour Holter monitoring. Significantly higher number and longer total duration of ischemic episodes was shown in the GERD (+) group – *Tab. 4*. The impact of reflux on the ANS activity was assessed in cases, when no recurrent refluxes were detected in control compartment (10 min before the reflux) and in 2 following 10-minutes long compartments, starting from the beginning of reflux. The existence of multiple reflux episodes in short time would interfere with the interpretation of collected data. Spectral HRV analysis was performed only when ECG recording was technically good and enabled identification of more than 95% R waves during the monitoring period as of sinus origin. Considering criteria presented above, 85 PR were selected for analysis: mean duration 16.82 min; (5.10-76.90 min); SD 14.90. Spectral HRV analysis was performed in 3 time intervals for each reflux. In every time interval 5 components of spectral HRV analysis were described (*Tab. 5*). *Tab. 6* shows the comparison of all components of spectral HRV analysis in studied time intervals. There were no significant differences in range of VLF i TP in all time intervals. Drop of LF and rise of HF did not reach the statistical significance, but there was a trend in control (-1) and study (0) compartment. Comparison of LF/HF (sympathovagal balance), however, showed statistically significant ($p < 0.036$) decrease of LF/HF in study compartment as compared to the control one. Comparison of LF/HF in compartments (-1) i (0) with compartment (1) did not show any differences.

Discussion

The pH-metric criteria of GERD have been found in almost half of patients (46%) in the studied group of 50 patients with

Table 5. **The values of spectral HRV analysis components in 3 time intervals, (-1) control interval before the reflux, (0) first 10 minutes from the beginning of reflux, (+1) successive 10 minutes following compartment 0**

variable	mean	SD (standard deviation)	minimum	maximum	mediana
VLF(-1)	814.38	1178.03	68.70	8770.84	487.92
LF(-1)	197.57	305.64	11.50	1938.08	101.74
HF(-1)	85.74	144.53	4.18	943.54	38.36
LF/HF(-1)	3.23	2.20	0.49	10.88	2.54
TP(-1)	1106.79	1480.35	108.86	11206.78	707.33
VLF(0)	825.38	1007.37	22.15	6694.10	493.27
LF(0)	183.70	286.05	13.39	1860.85	94.43
HF(0)	86.19	142.14	3.08	964.91	37.20
LF/HF(0)	2.94	1.90	0.17	8.29	678.34
TP(0)	1100.73	1193.94	43.51	6864.01	2.38
VLF(+1)	834.00	1138.00	22.15	7046.88	455.30
LF(+1)	196.19	451.24	13.39	3870.29	97.35
HF(+1)	81.56	180.58	4.00	1600.58	36.74
LF/HF(+1)	3.16	2.42	0.20	10.16	2.31
TP(+1)	1119.20	1416.71	43.51	8066.23	707.78

LF – low frequency [ms^2] range 0.5-0.05 Hz: component of sympathetic nervous system activity; HF – high frequency [ms^2] range 0.15-0.5 Hz: component of parasympathetic nervous system activity; VLF – very low frequency [ms^2] range <0.05 Hz – importance of this component isn't well known, it may express the activity of renin – angiotensin system and thermoregulation; LH/HF – temporary activity of ANS (sympathovagal balance); TP– total power [ms^2]. Data analysis – SPSS

Table 6. **Analysis of spectral HRV components variability in studied time intervals**

	A	B	C	p
VLF(-1)vsVLF(0)	43	42	85	0.7876
VLF(-1)vsVLF(1)	47	38	85	0.8833
VLF(0)vsVLF(1)	44	41	85	0.7342
LF(-1)vsLF(0)	52	33	85	0.0793
LF(-1)vsLF(1)	46	39	85	0.1984
LF(0)vsLF(1)	41	44	85	0.6820
HF(-1)vsHF(0)	36	49	85	0.0816
HF(-1)vsHF(1)	43	42	85	0.8764
HF(0)vsHF(1)	47	38	85	0.1054
LF/HF(-1)vsLF/HF(0)	51	34	85	0.0353*
LF/HF(-1)vsLF/HF(1)	43	41	85	0.7146
LF/HF(0)vsLF/HF(1)	36	49	85	0.2385
TP(-1)vsTP(0)	42	43	85	0.7342
TP(-1)vsTP(1)	46	39	85	0.6454
TP(0)vsTP(1)	43	42	85	0.6917

LF – low frequency [ms^2] range 0.5-0.05 Hz: component of sympathetic nervous system activity; HF – high frequency [ms^2] range 0.15-0.5 Hz: component of parasympathetic nervous system activity; VLF – very low frequency [ms^2] range <0.05 Hz – importance of this component isn't well known, it may express the activity of renin – angiotensin system and thermoregulation; LH/HF – temporary activity of ANS (sympathovagal balance); TP – total power [ms^2]

A: in compared pair first parameter value greater then the second
B: in compared pair first parameter value smaller then the second
C: general number of compared pairs
(Wilcoxon Matched-Pairs Signed-Ranks Test)
* statistically significant

angiographically confirmed ischemic heart disease. Presented results are correspond with the observations of other authors, already quoted in the introduction [3-5]. One of the possible explanations of frequent coexistence of both conditions are common risk factors, both occur more often in advanced age, among smokers and patients with visceral obesity [11]. In 1983 Mellow et al. described the impairment of coronary flow as the result of acidic stimulation of esophagus. In that study coronary flow was evaluated with Doppler transducer located in the left anterior descendent artery [12]. Results of Mellow's study were confirmed by Chauhan et al. [6,7]. In the present study we have shown that spontaneous acidic gastroesophageal reflux may trigger the myocardial ischemia. In GERD (+) patients there were more incidents of ST depression in ECG and their total time was significantly longer than in GERD (-) patients. Lux et al., using the simultaneous ECG and esophageal pH-metry monitoring in 15 patients with atherosclerotic lesions in coronary arteries showed time-dependence of 40% ST depression episodes with esophageal pathology [3]. The mechanism of myocardial ischemia increase by the experimental acidic stimulation of esophagus or spontaneous reflux is probably due to esophagocardiac reflex [6,7].

Frequency domain analysis of HRV is considered to be the best semi-quantitative method of ANS activity evaluation [10,13,14]. There are two methods of analysis: long term recording, used in for global assessment of ANS activity and short term recording, to assess the short term changes of vegetative system components and their balance [10]. According to the results of latter type of spectral HRV analysis, an attempt to explain the impact of PR on temporary activity of vegetative system was undertaken. The results of presented investigation did not show any differences in range of TP and LF components of spectral HRV analysis in studied time intervals. We observed the simultaneous decrease of LF component and increase of HF in study interval. Although neither change alone was statistically significant, this constellation caused statistically significant drop

of LF/HF ($p < 0.036$) before and during PR. Results indicate the short term shift of ANS balance towards its parasympathetic during the pathological gastroesophageal reflux (PR) and showed induction of the esophago-cardiac reflex by PR. Other authors also showed impairment of ANS function in patients with GERD. Blaut et al. found the disturbances of vegetative system in patients with GERD. Those authors, using the method of short term recording showed significant reduction of LF and HF in GERD patients in comparison with healthy individuals [13]. Campo et al. observed reduced activity of sympathetic system in patients with GERD, furthermore, they reported a reverse correlation between the activity of sympathetic system and the total duration of reflux [15]. Interesting results reported Tougas et al. in the group of patients with angina-like chest pain of esophageal origin (acid sensitive patients). Half of the studied patients fulfilled the pH-metric criteria of GERD. The authors showed higher basal heart rate and lower activity of vagal nerve in this group of patients in comparison to control. Stimulation of esophagus with hydrochloric acid caused the significant increase of parasympathetic component HF and decrease of LF/HF during the provocation and return to initial status directly after the infusion [16]. Results of the present investigation show, that PR causes similar alteration of ANS activity, as the one caused by experimental acidic stimulation of esophagus. Patients with esophagus motility disorders may also have the dysfunction of ANS. Pirtniecks et al. found the ANS disorders, mainly of the parasympathetic system, in patients with so called nonspecific esophageal motility disorders [14].

Significance of HRV has been thoroughly investigated in cardiovascular disorders. In 1987 Kleiger et al. showed, that decreased parameters of HRV are the independent risk factor after the myocardial infarction [17]. Dilaveris et al. observed the activation of sympathetic system only in patients with post-exercise myocardial ischemia [18]. The comparison of the quoted results with the results of our study shows that ischemic episode results in different alteration of ANS activity than the one caused by gastroesophageal reflux.

Conclusions

1. Gastroesophageal reflux disease is frequent condition in patients with angiographically confirmed ischemic heart disease. Coexistance of GERD in these patients may predispose to myocardial ischemia.

2. Gastroesophageal reflux may cause the shift of sympathovagal balance towards its parasympathetic component. This mechanism may induce esophago-cardiac reflex, leading to diminished myocardial perfusion.

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