Oesophageal acid stimulation in humans: Does it alter baroreflex function?

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The aim of this study was to investigate if oesophageal acid stimulation (Bernstein test) had an influence on heart rate and blood pressure variability and baroreflex gain.

We compared the cardiovascular responses in 10 patients with established gastro-oesophageal reflux disease (Group 1) and 10 control subjects (Group 2) during oesophageal saline and 0.1 mol/l hydrochloric acid instillation. Indices of heart rate and blood pressure variability and baroreflex gain (derived from linear spontaneous sequences and cross spectral analysis) were calculated. In Group 1 the standard deviation of RR intervals (SDRR: 46 ms vs. 51 ms, p=0.030) and the root mean square of successive differences (RMSSD: 24 ms vs. 26 ms, p=0.027) were significantly lower during acid infusions, than during saline. We found no significant difference in minimum, maximum and mean RR intervals and systolic blood pressures and in the percentage of RR intervals, which differed from adjacent cycles by more than 50 ms (PNN50). The power spectra of RR intervals in the high frequency band tended to be lower during acid infusion (p=0.055). There was no significant difference in blood pressure spectra, neither in low nor in high frequency band. In Group 2 there was no significant difference between any parameters measured during acid and saline. The baroreflex gain was not changed during the studied conditions in any group.

Neither increased vagal tone, nor increased vagal variability occurred and the baroreflex gain was not altered during oesophageal acid stimulation.

Keywords: autonomic nervous system, baroreflexes, oesophago-cardiac reflex

Several physiological relationships exist between the upper gastrointestinal tract and the cardiovascular system. It is known for a long time that manipulations in the larynx, pharynx and the oesophagus (e.g. during intubation, endoscopy) can cause severe

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cardiac arrhythmias, especially bradycardias and even cardiac arrest (5, 10). Also, there exists a type of syncope, which occurs in relation to swallowing, and which seems to be related to oesophageal distension. In the past few years the changes in coronary blood flow in relation with gastro-oesophageal diseases have attracted new clinical interest. The so-called 'linked angina' is supposed to have oesophageal origin (4, 9). Despite the clinical and experimental observations, the underlying mechanisms in these syndromes/reflexes are not fully investigated. It is also unclear weather these reflexes are physiological phenomena or they involve pathological processes. They are simply regarded as vago-vagal reflexes. The anatomical basis is that both the sensory and the motor fibers innervating the upper gastrointestinal tract travel with the glossopharyngeal or the vagus nerve. Both nerves terminate in the nucleus of the solitary tract, where specific connections exist between them and divisions of the autonomic nervous system. There are three hypotheses explaining the cardiovascular responses to gastrointestinal stimulations (5). First, mechanical factors, which directly irritate the heart or the carotid sinuses or their nerve supply, could be responsible. The second theory is based on the concept of ephaptic crosstalk, a non-synaptic communication between peripheral nerve fibers. The third theory assumes central 'crosstalk' within the medulla. According to this hypothesis, sensory information arising from the upper gastro-intestinal tract makes contacts within the brainstem, and terminates on cardiovascular interneurons. In that way it can affect the heart rate, blood pressure and the respiratory system (5).

The aim of our study was to investigate if baroreflex mechanisms were involved in these reflexes, and get further insight into the reflex relationship between the oesophagus and the cardiovascular system in normal conditions and in case of gastro-oesophageal reflux disease (GERD).

Methods

The study population consisted of 10 patients (5 men, 5 women, aged 48±14 years) with GERD (Group 1) and 10 control patients (6 women, 4 men, aged 41±13 years) (Group 2). The diagnosis of GERD was based on endoscopic findings, according to the Savary-Miller criteria and on 24-h oesophageal pH monitoring. All the subjects were informed and gave their informed consent for the participation in the study. The study protocol was approved by the Ethical Committee of the University of Szeged.

All measurements were made in a quiet room after 10–12 hours of fasting. The subjects' breathing was paced at 15 min (0.25 Hz). A thin nasogastric tube was inserted into the oesophagus and positioned above the lower oesophageal sphincter. All studies started following a 15-min resting period in semi-recumbent position. The subjects were familiarised with the procedure by including a 10-min period of saline instillation. This session was not included into further analyses. Subsequent to the familiarisation active study was performed by 10–10 minutes of oesophageal instillation of 100 ml volumes containing either isotonic saline or 0.1 mol/l hydrochloric acid

solution. The order of the challenges was randomised, and both the patients and the investigators were blinded regarding the identity of the infusates at the time of the study.

The ECG and blood pressure signals were continuously measured with a Marquette bedside monitor and with the Finapres non-invasive blood pressure monitor. Signals were recorded on-line and digitalized with 500 Hz by the Dataq/Windaq system. The data were analysed off-line using the WinCPRS software. All the calculations were performed from the last 5 minutes of the recordings. All recordings were peak detected automatically and checked by one of the investigators. Only one recording contained 1 premature beat and none contained artefacts. After the confirmation of peak detection heart rate and blood pressure variability indices (minimum, maximum and mean RR intervals, standard deviation of RR-intervals (SDRR), root mean square of successive RR differences (RMSSD), percentage of cardiac cycles differing from the adjacent cycles by 50 ms or more (PNN50); minimum, maximum and mean systolic blood pressure) were calculated (8), and search for spontaneous sequences and power spectral analysis of RR intervals (RRI) and systolic arterial pressure (SAP) were performed to assess baroreflex gain (7).

Spontaneous sequences were defined as three or more consecutive cycles of either systolic blood pressure elevation (up sequences) or fall (down sequences) coupled with RR interval changes in the same direction. The blood pressure change had to be at least 1 mm Hg/heart beat. No limit to RR interval changes was imposed. When the sequences were selected, linear regression analysis was performed, and only sequences with correlation coefficient >0.8 were accepted for further analysis. The phase shift was automatically set by the computer program according to the Yamamoto-Hughson method (7). For all of these sequences the slope of the function of delta RRI and delta SAP was calculated and averaged separately for up and down sequences.

Power spectral analysis was made for RRI and SAP fluctuations by using fast Fourier transformation. Traditional high and low frequency bands were set (HF: 0.15–0.5 Hz, LF: 0.05–0.15 Hz). To assess the association between RRI and SAP powers cross spectral analysis was performed, and only data with coherence >0.5 were used for alpha index calculation. Cross spectral alpha index was calculated as the square root of ratios of SAP and RRI powers. It was derived only in the low frequency band, because only low frequency alpha index is regarded as an estimate of baroreflex gain (7).

Statistical analysis. For statistical analysis we used the Sigmastat software. The variables during the two conditions were compared with paired T-test. Normal distribution of the data was checked in all instances, and in cases of skewed distribution non-parametric tests, i.e. Wilcoxon signed rank tests were performed. Level of significance was set at p<0.05.

Results

Investigating the results of patients with gastro-oesophageal reflux disease (Group 1) we found significant differences between the SDRR (46±23 ms vs. 51±25 ms, p=0.030) and the RMSSD (37±34 ms vs. 45±40 ms, p=0,027) values, these parameters were lower during acid, than during saline infusions. The RR interval HF spectrum tended to be lower (p=0.055) during acid stimulation, however this difference did not reach statistical significance. No other indices of heart rate and blood pressure variability or blood pressure power spectra showed significant differences. Of importance, no differences in baroreflex gains calculated from the spontaneous "up" and "down" sequences were found between acid and saline stimulations. Nor did the LF alpha index differ between the two study conditions. In Group 2 (control) none of the measured parameters changed during acid instillation compared to saline (Table I). With regard to the known diversity of the studied parameters among healthy individuals, no direct comparisons were done between the two groups.

Discussion

Our findings suggest that the baroreflex gain is not altered during oesophageal acid stimulation despite significant changes in certain indices of heart rate variability.

The decreases in SDRR, RMSSD and in the high frequency RR interval power spectra in GERD patients may indicate vagal withdrawal. However, in some circumstances the heart rate variability can dissociate from parasympathetic tone, and indices of heart rate variability do not necessarily reflect vagal activation. It has been described by Goldberger et al. (6) that during phenylephrine infusion despite parasympathetic activation, the time domain indices of heart rate variability and the high frequency power of RR intervals decreased.

It seems that the different types of oesophageal stimulation result in different effect on autonomic neural activity. Bortolotti et al. (2) studied patients with diffuse oesophageal spasm during swallowing. They found that while dry swallows induced tachycardia, the deglutition of solid bolus elicited a biphasic response consisting of initial tachycardia followed by a phase of bradycardia. Oesophageal balloon inflation caused a significant decrease in heart rate, which was more intense in patients with oesophageal spasm than in control patients. Tougas et al. (11) investigated the effect of electrical and mechanical oesophageal stimulation on heart rate variability in healthy volunteers. They found a small but significant decrease of heart rate and a pronounced decrease of the mean variance of instantaneous heart rate both during electrical and mechanical stimulation of the distal oesophagus. They also found an increase in HF power of RR intervals accompanied with significant decrease in LF power.

Table I

Heart rate and blood pressure variability and values of baroreflex gain derived from different methods (mean±SD)

	Group 1		Group 2	
	saline	acid	saline	acid
Rrmin (ms)	741 ± 117	756 ± 130	716 ± 64	720 ± 61
Rrmax (ms)	1049 ± 197	1004 ± 197	974 ± 106	974 ± 104
Rrmean (ms)	896 ± 131	881 ± 151	852 ± 108	856 ± 89
SAPmin (mm Hg)	120 ± 18	125 ± 22	134 ± 15	135 ± 18
SAPmax (mm Hg)	146 ± 17	149 ± 19	158 ± 18	164 ± 26
SAPmean (mm Hg)	135 ± 17	137 ± 20	146 ± 17	150 ± 23
SDRR (ms)	51 ± 25	46 ± 23*	43 ± 17	42 ± 17
RMSSD (ms)	45 ± 40	37 ± 34*	32 ± 13	30 ± 14
PNN50 (ms)	17 ± 29	15 ± 26	11 ± 14	10 ± 13
RR LF (ms^2)	523 ± 428	631 ± 528	413 ± 276	421 ± 394
RR HF (ms^2)	1543 ± 2900	890 ± 1449	589 ± 580	558 ± 600
SAP LF ($mm\ Hg^2$)	4.6 ± 3.6	5.0 ± 3.1	3.7 ± 2.6	5.6 ± 4.7
SAP HF ($mm\ Hg^2$)	2.0 ± 1.6	2.2 ± 1.3	3.4 ± 2.5	2.6 ± 1.8
upBRS (ms/mm Hg)	9.4 ± 6.5	7.5 ± 2.9	10.6 ± 5.6	10.8 ± 5.5
downBRS (ms/mm Hg)	16 ± 11	15 ± 12	12.1 ± 6.5	10.4 ± 4.9
LF alpha (ms/mm Hg)	13 ± 10.2	15.6 ± 15.8	13.0 ± 7.3	10.3 ± 4.6

Group 1: patients with GERD
Group 2: control patients
LF: low frequency band
HF: high frequency band
upBRS: BRS values derived from up sequences
downBRS: BRS values derived from down sequences
LF alpha: cross spectral BRS in the low frequency band
* significant differences between the study conditions, $p < 0.05$

They explained their findings by amplified cardiac vagal modulation and decreased sympathetic effect. These authors however speculated that their findings could be related to the entrainment in high frequency band (11). To study this possibility further, they assessed the effects of different electrical stimulation frequencies on the spectral indices of heart rate variability. In this study the stimulation frequencies ranged from 0.1 Hz to 1.0 Hz and resulted in increase in HF and decrease in LF powers regardless of the stimulation frequency (1).

It has also been suggested that the so-called linked angina originates from the oesophagus. It is supposed that oesophageal reflux or motility disorders can precipitate myocardial ischemia. This phenomenon, though rare (9), may be caused by neural mechanisms. Chauhan et al. (4) observed in patients with angiographically established coronary heart disease that acid instillation into the oesophagus caused coronary flow reduction, measured by intracoronary Doppler catheter. In the group of heart transplant recipients there was no change in flow, so they assumed neural mechanism, the paradoxical effect of increased vagal tone and acetylcholine on coronary arteries

with endothelial dysfunction (4). They also demonstrated that oesophageal acid stimulation can reduce coronary blood flow in angiographically normal arteries in syndrome X patients (3).

In summary, the BRS values calculated with different techniques were not altered by oesophageal acid stimulation. As indicated before, our results can be interpreted as evidence of vagal withdrawal and no consequence can be drawn regarding sympathetic activity. What is clear form the data, that neither increased vagal tone (mean RR interval), nor increased vagal variability (SDRR, PNN50, RMSSD) occurred. Therefore the vago-vagal hypothesis, as the sole mechanism of GERD-linked syndromes is questionable. Direct muscle sympathetic nerve studies may help to clarify the issue.

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