Coronary spasm reflects inputs from adjacent esophageal system

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Manfrini, Olivia, Gabriele Bazzocchi, Alessandra Luati, Alberigo Borghi, Paola Monari, and Raffaele Bugiardini. Coronary spasm reflects inputs from adjacent esophageal system. Am J Physiol Heart Circ Physiol 290: H2085–H2091, 2006. First published December 30, 2005; doi:10.1152/ajpheart.00925.2005.—Mechanisms underlying coronary spasm are still poorly understood. The aim of the study was to assess the hypothesis that fluctuations in the development of coronary spasm might reflect inputs from the adjacent esophageal system. We enrolled patients admitted to the coronary care unit for episodes of nocturnal angina. Seven patients with variant angina and five with coronary artery disease (CAD) had concurrent ECG and esophageal manometric monitoring. ECG monitoring documented 28 episodes of ST elevation in variant angina patients and 16 episodes of ST depression in CAD patients. Manometric analysis showed that esophageal spasms resulted remarkably more frequently in variant angina patients (143 total spasms; individual range 9–31) than in CAD patients (20 total spasms; individual range 0–9; P < 0.01). Time series analysis was used to assess fluctuations in the occurrence of abnormal esophageal waves and its relationship with spontaneous episodes of ST shift. Episodes of esophageal spasm in CAD were sporadic (<1 in 30 min) and not related to ECG-recorded ischemia. In the variant angina group, esophageal spasms were time related to ischemia (>1 into 5 min before ECG-recorded ischemia) (P < 0.05). A bidirectional analysis of causal effects showed that the influence processes between esophageal and coronary spasms were mutual and reciprocal (transfer function model, P < 0.05) in variant angina. We concluded that in variant angina patients, episodes of esophageal spasms and myocardial ischemia influenced each other. Mechanisms that cause esophageal spasm can feed back to produce coronary spasm. Coronary spasm may feed forward to produce additional episodes of esophageal spasm.

angina; vasospasm; autonomic nervous system

CORONARY ARTERY SPASM can be the underlying cause of angina pectoris and ischemia in patients with normal coronary arteries or mild atherosclerosis (12, 18). Numerous studies (25, 27) have reported that either sympathetic or parasympathetic stimulation through cardiac reflexes can produce segmental abnormality in vasomotor tone leading to transient focal coronary occlusion. Abnormalities in autonomic nervous regulation have been demonstrated as well in patients with many esophageal disorders (6, 8). These observations suggest a strict relationship between the heart and the esophageal system. Accordingly, neural reflex arcs from the esophagus to the heart have been shown in both animals and humans (7, 10, 17, 19). On the one hand, esophageal provocation with ice water, hydrochloric acid, and balloon inflation may influence coronary blood flow in humans (7, 17). On the other hand, patients with chest pain and normal coronary arteries are often found to develop esophageal spasm during a variety of cardiac procedures (17).

The current study was designed to address the hypothesis that the variability in the spontaneous onset of coronary spasm might be triggered by inputs coming from the esophageal system.

I am a 40-year old lawyer, and am generally healthy and fit. However, I get a crushing chest pain every now and then. . . . I go to the emergency department to be sure I’m not having a heart attack. After the last visit, I had a coronary angiogram to try to see whether I had heart problems, but it showed no evidence of atherosclerosis. . . . I am still nervous that the test might have missed something. (T. H. Lee, Ref. 15a, p. 7).

METHODS

Patients and study design. Patients admitted to the coronary care unit for episodes of rest nocturnal angina accompanied by transient ST-segment elevation or ST-segment depression of the ECG were invited to take part in the study. Patients with myocardial infarction (creatine kinase >2 times upper limit), cardiomyopathy, valvular heart disease, congestive heart failure, renal dysfunction, and atrial fibrillation were excluded. Patients were also excluded from the study if they were receiving acid-reducing medications. Patients were treated with heparin, intravenous nitrates, aspirin, and β-blockers. Esophageal motility and ECG were monitored in all patients during bed stay in the coronary care unit. Patients underwent coronary angiography within 4 days of admission. They were grouped according to the criteria shown in Fig. 1. Briefly, on the basis of the angiograms (visual estimation), patients with left main disease were dropped from the study. Patients with >50% lumen stenosis in at least one epicardial coronary artery and ST-segment depression on the ECG at hospital admission were grouped as coronary artery disease (CAD). Patients with <50% lumen stenosis and ST-segment elevation on the ECG at hospital admission underwent an ergonovine test. When the ergonovine test provoked a coronary vasospasm, those patients were grouped as variant angina. Informed written consent was obtained in all cases. This study was reviewed and approved by the Ethical Committee of University of Bologna, Bologna, Italy.

Esophageal manometric study. An esophageal manometric recording was obtained simultaneously with an ECG recording. Esophageal manometric studies were performed with the use of a six-lumen polynvinyl catheter (external diameter, 4.5 mm; intraluminal diameter, 0.8 mm; Arndorfer Specialties, Greendale, WI). The pressure recording was made from six radially positioned side holes at 5-cm intervals. The manometric catheter was introduced transnasally into the stomach and was then withdrawn at 0.5-cm increments by using a standard station pull-through technique so that the lower esophageal sphincter pressure could be recognized during end expiration. The four proxi-

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mal recording sites were then repositioned into the esophageal body, the fifth recording site was positioned at the lower esophageal sphincter level, and the more distal left was in the stomach. The esophageal catheter was connected to a low-compliance pneumohydraulic perfusion system and perfused with water at a constant rate of 0.5 ml/min. Pressure signals were acquired on a computerized system at a sampling frequency of 20 Hz and processed using specialized software (RedTech). All patients were studied in the supine position after an overnight fast. During the esophageal manometric recording, a swallow marker was employed to recognize the occurrence of spontaneous and second swallows (causing deglutitive inhibition) and to provide evidence of secondary peristalsis (propagating contractions not following any swallow). A sensor belt on the neck was used in all patients. Starting time of monitoring ranged between 9:00 AM and 10:30 AM. A light lunch was given after 90 min. On the basis of the manometric features, esophageal abnormalities were categorized according to previously accepted criteria (1, 21).

ECG analysis. The ECG was recorded with the use of a two-channel (lead CM5 and modified lead II) tape recorder during the esophageal manometric study. Patients were asked to keep a detailed diary of their activities during monitoring, including the time they were reading and the time they were watching television, and of symptoms such as chest pain. Two expert cardiologists analyzed the tapes with a Del Mar Avionics Acuplus (model 363). ST changes of 1.5 mm (0.15 mV) or more as measured at 80 ms after the J point lasting for 1 min or more were defined as significant ST-segment shifts. We analyzed the number and the duration of the ischemic episodes for each ECG recording.

Ergonovine test. Patients received conscious sedation (diazepam) as needed. Diagnostic coronary angiography was performed in all patients by the Judkins technique. After the coronary angiography was performed, in those patients having ST-segment elevation at enrollment, ergonovine testing was performed. Graded doses of ergonovine (100, 200, and 300 μg) were given intravenously at 5-min intervals. Angiograms were taken after each dose. The ergonovine dose was upgraded only if coronary spasm did not occur. Intracoronary isosorbide dinitrate (1–2 mg) was administered at the end of the study. Twelve-lead ECG and arterial blood pressure were continuously monitored during the procedure.

Statistical analysis. Results are expressed as means ± SD. Associations were analyzed by using t-test for unpaired observation. Values of P < 0.05 were regarded as significant.

We used linear transfer function models (y_t = g x_t + u_t) to assess whether one variable (input, x_t)–abnormal esophageal wave or ST-segment change–could significantly influence the other (output, y_t) (2): abnormal esophageal wave on ST-segment change and ST-segment change on abnormal esophageal wave. Influences could be immediate or delayed in time. Statistical evidence of a self-propagating feedback reaction between coronary arteries and esophagus was subsequently evaluated.

Other influences apart from the input (coronary arteries or esophagus) could affect the output (esophagus or coronary arteries): the combined effect of these influences is represented by the noise of the model (u_t), described by a stochastic process. In the empirical analysis, the identification of the stochastic process u_t was performed using the standard Box and Jenkins (3) iterative procedure consisting of four steps: 1) preliminary analysis of the observed series; 2) identification of a model in the class of the Autoregressive Integrated Moving Averages (ARIMA) (p, d, q)–processes of the form (1 − B)^d u_t = φ_1 u_{t−1} + ... + φ_p u_{t−p} + α_t − θ_1 α_{t−1} − ... − θ_q α_{t−q} where B is the lag operator such that B^d u_t = u_{t−d} and α_t is a white noise process, i.e., with zero mean, finite and constant variance, and null covariance; 3) estimation of the parameters; and 4) diagnostic checking. The significance of the parameter g accounting for the impact on the input over the output was evaluated in the estimation phase rejecting estimates with P > 0.05. Identification of a model in the class of the ARIMA processes was based on the global and partial autocorrelation functions of the stationary time series, as a comparison with those of the theoretical ARIMA processes. The estimation of the ARIMA parameters and coefficient g was automatically performed with the maximum likelihood iterative method. The diagnostic checking was based on the analysis of the residuals, which resulted as uncorrelated (the Ljung-Box statistic test).

Statistical evaluation was performed with the use of SPSS-Win 11 (Statistical Package for the Social Sciences, Chicago, IL).

RESULTS

Ninety-eight patients were asked to participate in the study. Of these, 69 refused because of the nose-esophageal tube placement. Twenty-nine patients agreed to participate in the study, but 17 patients did not complete it. The withdrawal of these patients was due to difficulties with the placement of the nose-esophageal catheter (2 patients) and discomfort after its placement (14 patients). One patient was found to have transient ST elevation as well as 80% coronary lumen stenosis and therefore was not considered eligible for further investigation. Twelve patients completed the study (8 men and 4 women). Five patients with coronary lumen stenosis >50% were grouped as CAD, whereas seven patients showing normal or near normal coronary arteries and documented coronary spasm with ST-segment elevation during the ergonovine test were grouped as variant angina. Patient characteristics are reported in Table 1.

Manometric and ECG analysis. Manometric and ECG recordings lasted >4 h (mean 363 min, range 270–461 min). None of the patients showed features for an established diagnosis of diffuse esophageal spasm, hypertensive lower esophageal sphincter, achalasia, and nutcracker esophagus (21). Two
patients in the variant angina group and one patient in the CAD group showed few nutcracker-like, peristaltic esophageal contractions not associated with ischemia. In addition, manometric studies showed a total of 163 abnormal motility events (Fig. 2), consisting of high-amplitude (>100 mmHg), simultaneous, nonperistaltic, and spontaneous (not induced by swallowing) contractions occurring in at least two contiguous pressure recording sites, lasting ≥10 s (median amplitude was 117 mmHg, range 105–225 mmHg; and median duration was 13 s, range 10–17 s). The esophageal pressure approximated baseline pressure between contractions. Table 2 gives the number of esophageal spasms and ST-segment changes in each patient. Esophageal abnormalities resulted remarkably more commonly in patients with variant angina (total 143, individual range 9–31) than in those with CAD (total 20, individual range 0–9; *P < 0.01). The ECG recording showed 28 episodes of ST elevation (mean 4 ± 4.6) in patients with variant angina and 16 episodes of ST depression in patients with CAD (mean 3.2 ± 2.6).

The episodes of ECG-recorded ischemia and esophageal spasms were either symptomatic or asymptomatic. Patients with CAD had four episodes of chest pain always associated with ECG-recorded ischemia, but they did not have abnormal esophageal waves. Patients with variant angina reported 12 chest pain attacks. Specifically, nine episodes of chest pain were documented simultaneously with ST shifts and abnormal esophageal spasms; two episodes developed concurrently with ECG-recorded ischemia but not esophageal spasm; and one episode was concomitant with esophageal spasm 7 min before ECG-recorded ischemia.

The mean heart rate of ECG recordings ranged from 52 ± 6 to 85 ± 11 beats/min in the variant angina group and from 48 ± 5 to 72 ± 9 beats/min in the CAD group (*P = not significant). The averaged heart rate before the first ischemic attack (averaged value of 30 min) was higher in the variant

Table 1. Clinical characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>Variant Angina</th>
<th>CAD</th>
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</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>5 (71)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Cardiovascular factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (40)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (40)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1 (14)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descendig</td>
<td>5 (71)*</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>1 (14)*</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>2 (29)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Values represent number of individuals; values in parentheses are percentages of individuals within the group. CAD, coronary artery disease. Ages of the two study groups are the following: variant angina (n = 7 patients), 56.7 ± 6.6 yr (mean ± SD); and CAD (n = 5), 64.4 ± 7.3 yr. *One patient showed focal coronary vasoconstriction in both left anterior descending and left circumflex coronary arteries.

Table 2. Number of episodes of ES and ST-segment changes

<table>
<thead>
<tr>
<th>Patient</th>
<th>ES</th>
<th>ST-segment elevation</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
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<td>24</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>ES</th>
<th>ST-segment depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>6</td>
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<td>10</td>
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<td>1</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

ES, esophageal spasm.

Fig. 2. Example of esophageal manometric recording obtained during episode with ST elevation: E1, E2, and E3, recording sites spaced 5 cm apart in the esophageal body. Swallow (sw) occurrences are indicated by closed circles. Seven regular swallow-induced sequences of peristaltic contractions come before a giant contraction (arrow), which occurs simultaneously at the 3 recording levels showing duration between 10 and 20 s.
angina group than in the CAD group (87 ± 6 vs. 70 ± 5 beats/min; P < 0.05).

Time series analysis of abnormal esophageal spasm and ST-segment shift. The preliminary analysis showed that in patients with variant angina, 24 (86%) of the episodes of ST shifts were concurrent or slightly (<5 min) preceded by the occurrence of at least one abnormal esophageal spasm. Episodes of esophageal spasm often clustered (>3 episodes within 5 min). Conversely, the few episodes of esophageal spasm recorded in CAD were sporadic (<1 in 30 min) and not time related to ECG-recorded ischemia. Most patients with variant angina (5/7) had >2 episodes of ST-segment shifts and esophageal spasms within 30 min and were eligible for the further steps of the time series analysis (Figs. 3 and 4).

The results of the analysis are reported in Table 3. Table 3 shows the significance of the input variable and its relationship with the behavior of the output time series. The stochastic model for the noise is reported as well, mainly for evaluation of reproducibility of the analysis. The results were as follows.

1) Variant angina patients 1, 2, and 5 showed evidence of a chain reaction between coronary artery and esophageal spasms. Indeed, a significant P value was achieved either when the abnormal esophageal wave (P = 0.050, P < 0.001, and P = 0.008) or the ST-segment change (P = 0.020, P = 0.028, and P < 0.001) was the input variable.

2) Variant angina patients 3 and 4 showed evidence of a self-propagating situation whereby the esophageal contraction could aggravate coronary artery spasm (P < 0.001 and P = 0.004) with no feedback from the coronary system to the esophagus.

Analysis of number and duration of myocardial ischemic episodes. We searched for discriminating factors accounting for the difference between patients with and without feedback reaction. We approached this aim by evaluating the power of the esophageal and cardiac stimuli. The power of esophageal spasm was expressed as the ratio between the number of esophageal spasms and the range of time in which they occurred (ES-no/tES in min). The power of coronary spasm was expressed as the ratio between a dual-task input process (number of ST-segment shift multiplied by their length) and the range of time in which ST episodes occurred (ST-no × ST-length/tST in min). The ratios between the two measures (ES-no/tES)/(ST-no × ST-length/tST) are reported in Table 4. When the ratio was low (<0.20), both coronary arteries and esophagus acted as input and could significantly influence each other. When the ratio was high (>0.20), only the esophagus could significantly influence the heart.

Data may be summarized as follows. All variant angina patients showed episodes of abnormal esophageal waves. In five of seven patients with variant angina, esophageal spasms gave origin to a self-propagating process that influenced coronary spasm and myocardial ischemia. Of these, three patients had feedback reaction. Analysis of the power of the cardiac stimuli related to the esophageal spasm documented that a feedback reaction from the coronary arteries to the esophagus could be obtained when one of the following conditions was achieved: a high number of ischemic episodes, and/or ischemic episodes of long duration, and/or relatively frequent ischemic episodes occurring within a short window of time.

DISCUSSION

The current study demonstrates that esophageal and coronary artery spasms are strictly interconnected in patients with variant angina. The relationship consists of a self-propagating situation whereby the esophageal contraction aggravates the abnormality in coronary motility, which in turn may induce further esophageal spasms.

Time series analysis of coronary and esophageal spasm. This is the first study that focuses on a possible time-dependent relationship between spontaneous episodes of esophageal and coronary spasm. To address this aim, we used time series

Fig. 3. Findings of variant angina in patient 2: heart rate [HR, in beats/min (bpm)], ST-segment trend, occurrence of esophageal spasms (ES), and chest pain episodes. Findings were obtained during 331 min of ECG and esophageal motility monitoring.

Fig. 4. Findings of coronary artery disease in patient 11: HR, ST-segment trend, ES, and chest pain episodes. Findings were obtained during 286 min of ECG and esophageal motility monitoring.
A time series is a record of consecutive observations on the same phenomenon. In contrast to the analysis of random samples, a time series analysis is based on the sequence of the observed values of the data set. The analysis accounts for data points taken over time and identifies possible time relation and dependence among the observations.

In patients with obstructive CAD, we could not prove a link between myocardial ischemia and esophageal spasm. Conversely, in variant angina, episodes of ECG-recorded ischemia were time dependent on esophageal spasm. Every patient had his or her own individual time functional model according to his or her biological clock. Esophageal spasm was the primary event of the chain. Mechanisms that caused esophageal spasm fed back to produce coronary spasm, and coronary spasm often fed forward to produce additional episodes of esophageal spasm. The high number of ischemic episodes or their prolonged duration elicited the feedback reaction from the coronary arteries to the esophagus.

Cardioesophageal interaction: clinical observations. The assumption that some gastrointestinal factors may cause angina and myocardial ischemia has been postulated more than 50 years ago as “linked angina.” In 1956, Froment (9)

### Table 3. Results of transfer function models estimation in variant angina (coefficients and P values)

| Patient 1 | ARIMA (2,0,0) | \( \phi_1 \) | 0.78 | \( \phi_2 \) | -0.21 | \( \phi_3 \) | 0.09 | 0.050 |
| ARIMA (1,0,0) | \( \phi_1 \) | 0.71 | \( \phi_2 \) | 0.000 | \( \phi_3 \) | 0.000 | 0.000 |

### Table 4. Episodes of ES and myocardial ischemia in variant angina patients with and without feedback reaction

| Patient | ESn | Time* | STn | Duration, min | Time† | \((ES_n/|TST|)/(ST_n \times ST_{min})\) |
|---------|-----|-------|-----|---------------|-------|---------------------------------|
| 1       | 31  | 212   | 14  | 49            | 209   | 0.04                            |
| 2       | 26  | 291   | 4   | 16            | 75    | 0.12                            |
| 5       | 18  | 228   | 2   | 3             | 35    | 0.17                            |

Time is range between beginning of the first and the end of the last episodes of *ES and †myocardial ischemia, respectively. ESn and STn, number of ES and ST-segment shifts; \( t_{ES} \) and \( t_{ST} \), range of time (in min) in which ES and ST episodes occurred, respectively.
reported that heart disease was often associated with many gastrointestinal diseases that may concur to cause angina-like chest pain. In 1955, Kramer and Hollander (14) reported the occurrence of ST-segment depression in one patient undergoing esophageal balloon distension. In 1960, Roesler (22) described four patients having myocardial infarction after ingestion of cold liquids or after meat ingestion with consequent esophageal stimulation. After these early observations, many other studies (5, 7, 10) documented abnormalities of the esophageal motility in patients suffering myocardial ischemia. A recent work (13) indicates that in a group of 94 patients with esophageal dysfunction, 20% had subsequent cardiac events, including death and myocardial infarction at a 2-yr follow-up. The results of our study may help to explain the high proportion of cardiac events in patients affected by esophageal dysfunction and may substantiate the hypothesis of a pathophysiological link between gastrointestinal disorders and angina pectoris, at least in those patients affected by variant angina (9).

Cardioesophageal mechanisms of interaction. The time-dependent relationship between spontaneous esophageal and coronary spasm in variant angina patients supports the hypothesis that esophagus and coronary arteries could have a common cause underlying their spastic disorder. In the current study, the averaged heart rate before an ischemic attack (averaged value of 30 min) was significantly higher in the variant angina than in the CAD group. Some studies (15, 27, 28) have suggested that autonomic dysfunction with sympathetic hyperactivity could be the main cause of coronary spasm, but others (24) have denied this hypothesis. Our findings support the role of sympathetic activity as a contributing factor to the occurrence of spontaneous coronary and esophageal spasm.

Our data do not give information to localize the site and the causes of the pathological process. Neural reflex arcs from the esophagus and heart have been shown in both animals and humans (17, 19). Loss of ganglion cells in the intramural cardiac-esophageal plexuses might be speculated (11). Neural plexuses, however, are not readily accessible for routine biopsies.

Clinical implications. This study provides evidence that esophageal spasm is an undesirable event that triggers abnormal coronary vasconstriction and ischemia. This finding may have some clinical implications.

Diffuse esophageal spasm is a relatively rare disease of unknown etiology. When investigating patients with documented esophageal spasm, it seems important to take reasonable steps to try to exclude concurrent cardiac abnormalities, especially coronary artery vasospasm. Myocardial infarction, cardiac arrest, and sudden death can occur, although infrequently, with variant angina, even in the absence of obstructive coronary stenosis (4, 16).

Twenty-four-hour ECG monitoring may be appropriate for the evaluation of those patients with more frequent episodes of chest pain. The occurrence of transient episodes of ST-segment elevation can be critical in making the correct diagnosis. Presently, no widely accepted noninvasive test exists for eliciting vasospastic angina in the setting of normal or mildly obstructive coronary arteries (23). Nevertheless, reversible myocardial ischemia due to coronary vasospasm may be demonstrated by using exercise radionuclide perfusion scans and hyperventilation testing (4, 13, 20, 26).

In conclusion, the results of this study suggest looking very carefully at those patients with angina-like chest pain and esophageal spasm. Episodes of esophageal and coronary spasm influence each other in a mutual way.

REFERENCES


