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Cardioesophageal Reflex: A Mechanism for "Linked Angina" in Patients With Angiographically Proven Coronary Artery Disease

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Objectives. **The purpose of this study was to investigate the presence of a cardioesophageal reflex in patients with coronary artery disease that may explain the mechanism of "linked angina."**

Background. **It has been previously shown that esophageal acid stimulation can reduce coronary blood flow in patients with syndrome X, suggesting the presence of a cardioesophageal reflex in humans.**

Methods. **We studied the effect of esophageal acid stimulation on coronary blood flow in 14 patients with angiographically documented significant coronary artery disease and in 18 heart transplant recipients. Hydrochloric acid (0.1 mol/liter) and 0.9% saline solution were infused in random, double-blind manner (60 ml over 5 min) through a fine-bore tube positioned in the patient's distal esophagus, and coronary blood flow measurements were obtained after each infusion by use of a 3.6F intracoronary Doppler catheter positioned in the proximal left anterior descending coronary artery.**

Results. **Coronary blood flow was reduced significantly by esophageal acid stimulation in the coronary artery disease group (before acid 70.4 ± 14.3 ml/min, after acid stimulation 46.4 ± 19.1 ml/min [mean ± SD], $p < 0.01$). However, there was no significant difference in coronary blood flow during saline infusion (73.5 ± 15.3 vs. 72.5 ± 14 ml/min). Coronary blood flow in the heart transplant group was not affected by acid or saline infusion.**

Conclusions. **Esophageal acid stimulation can cause anginal attacks and significantly reduce coronary blood flow in patients with coronary artery disease. The lack of any significant effect in heart transplant recipients with heart denervation suggests a neural reflex.**

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It has long been suspected that esophageal disease may aggravate myocardial ischemia (1–3). Smith and Papp (4), coined the term *linked angina*, which implies that in patients with established coronary artery disease gastrointestinal factors cause attacks of genuine angina by mechanisms not obviously related to an increase in cardiac work. Pain is typically induced by stooping or after eating. Acid infusion into the esophagus has been shown to reduce significantly the exertional angina threshold in patients with coronary artery disease (5). There is also evidence that angina caused by esophageal acid stimulation most likely leads to myocardial infarction (6). However, the mechanisms responsible for these observations have not been clear.

We have shown previously that esophageal acid stimulation can reduce coronary blood flow in patients with syndrome X, suggesting the presence of a cardioesophageal reflex in humans (7). The presence of such a reflex in patients with coronary artery disease could explain the mechanism of linked angina. The aim of this study was to investigate the hypothesis that esophageal acid stimulation can reduce coronary blood flow in patients with coronary artery disease as a result of the presence of a cardioesophageal reflex.

Methods

Patients. The effect of esophageal stimulation on coronary blood flow was studied in 14 patients with coronary artery disease and in 18 heart transplant recipients.

Coronary artery disease group. Fourteen patients (12 men, 2 women) were studied. All patients had a history of chest pain typical of angina pectoris and had an electrocardiogram positive for angina pectoris on exercise. The coronary anatomy of all patients was known from previous coronary angiography. None of the patients had a clear history suggestive of gastroesophageal reflux. All patients had >50% stenosis of the right coronary artery or the circumflex coronary artery or both. The left main coronary artery was free of angiographic evidence of disease in all patients. The left anterior descending coronary artery was also free of angiographic evidence of disease in the proximal segment (up to the origin of the second diagonal) but

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had minor disease (<30%) in the distal segment in all patients. Patients with hypertension, diabetes mellitus, valvular heart disease or left ventricular hypertrophy were excluded from the study.

Heart transplant group. Eighteen (17 men, 1 woman) heart transplant recipients were studied. These patients did not complain of any chest pain and had coronary arteries free of angiographic evidence of disease.

Blood analysis. After an overnight fast, the patients' blood was analyzed for full blood count, serum urea and electrolytes and lipids on the morning of the study.

Echocardiography. Echocardiographic assessment was performed in all patients. Cross-sectional and M-mode assessments of the left ventricular posterior wall and septal thickness were made. Patients with a diastolic septal or posterior wall thickness >11 mm were excluded from the study to minimize any effect of left ventricular hypertrophy on coronary blood flow measurements.

Catheterization protocol. All patients fasted overnight for cardiac catheterization. All cardiac medications had been stopped for 48 h. Patients were allowed to use their glyceryl trinitrate tablets or spray for chest pain as required. However, if they experienced chest pain on the morning of the study, they were not included. A soft, fine-bore nasogastric tube was introduced through the nose after the nasopharynx had been sprayed with Lignocaine. The distal tip of the tube was positioned 35 cm from the nose. The position of the esophageal sphincter had been determined previously by manometry and was 35 cm distal in all patients. Patients were premedicated with 10 mg of diazepam before cardiac catheterization. Coronary angiography was performed by the Judkins technique through the right femoral artery in all patients. Coronary injections were performed manually with up to 8 ml of intracoronary radiopaque contrast medium (Niopam). Cine film recordings were performed in multiple projections. The proximal left anterior descending coronary artery was centered for optimal viewing after the initial angiograms had been obtained. To eliminate vasoactive effects of the contrast medium, at least 10 min were allowed to lapse before the coronary blood flow study.

Heparin sodium (10,000 U) was then given intravenously. An 8F angioplasty guide catheter was positioned at the left coronary ostium. Through this, a 0.014-in. (0.035 cm) guide wire was advanced into the distal part of the left anterior descending coronary artery. Using a monorail technique, a 3.6F 20-MHz Doppler-tipped catheter (Schneider) was then advanced over the guide wire and positioned in the proximal segment of the left anterior descending coronary artery. The Doppler catheter was then connected to a Millar velocimeter (model MDV-20, Millar Instruments). The Doppler catheter and the range-gate of the velocimeter were adjusted to obtain good quality phasic and mean coronary blood flow velocity signals. These signals were recorded on a Mingograf recorder (Siemens-Elema). Baseline mean rest and phasic coronary blood flow velocity were then recorded. Patients were instructed before the study to report any chest pain. For technical reasons, the electrocardiogram could only be recorded in leads II, V_2 or V_5.

Esophageal stimulation protocol. After the baseline recording of rest coronary flow velocity had been performed, esophageal stimulation with 0.1 mol/liter hydrochloric acid or 0.9% saline solution was started through the previously positioned nasogastric tube. A volume of 60 ml was given over 5 min. The order of stimulation (acid or saline solution) was determined by an independent technician and was not known to the patient or the investigator. After the infusion, coronary flow velocity was measured again. The coronary flow velocity was allowed to return to baseline, esophageal stimulation was then repeated using the other infusion (acid or saline solution) and the measurements were repeated as previously described. It was noted whether the patients with coronary artery disease experienced any chest pain and whether this was typical of their usual pain. The infusion was stopped immediately when the patient experienced typical chest pain or when the coronary blood flow velocity decreased by >50%.

Quantitative measurements. Quantitative coronary angiography was performed before and after the esophageal infusions in all patients. Quantitative measurements of the left anterior descending coronary artery diameter were obtained using digital electronic calipers (Sandhill Scientific Inc.). This method has been used previously to assess the arterial diameter of coronary vessels and has been described in detail (7–12).

Coronary sinus blood sampling. In all patients, the coronary sinus was intubated with a polyethylene 7F Sones catheter to sample blood before and after infusions for measurements of catecholamines and endothelin. The catheter tip was positioned ~2.5 cm from the os of the coronary sinus to minimize the risk of admixture of right atrial blood in the samples. A satisfactory catheter position was confirmed by the hand injection of the contrast medium. Samples were snap-frozen and then assayed with radioimmunoassay for endothelin-1 levels (13). Epinephrine and norepinephrine concentrations were measured by high performance liquid chromatography (14).

Ethical approval. The study was approved by the Huntingdon Health Authority Ethical Committee. Full written informed consent was obtained from all patients before the study.

Coronary flow calculations. Coronary flow velocity was recorded at rest and after the termination of each infusion according to esophageal stimulation protocol. The Doppler velocity recordings were corrected for changes in the arterial cross-sectional area to provide an estimate of volumetric flow. Estimates of coronary blood flow (Q) were made from measurements of mean coronary flow velocity (V) and vessel cross-sectional area (CSA):

$$Q = V \times CSA.$$

Cross-sectional area was calculated by the following equation:

$$CSA = \pi r^2,$$

where r = coronary artery radius as determined by quantitative analysis of the angiograms obtained in the preselected views.

Table 1. Clinical Characteristics of Study Patients

	CAD Group (n = 14)	Transplant Group (n = 18)
Age (yr)		
Mean	59	48
Range	52–67	23–61
Male	12	17
Female	2	1
Weight (kg)	74 ± 8	67.7 ± 10.2
Smoker	7	3
Hb (g/dl)	14 ± 1.1	11.5 ± 1.8
ESR (mm/h)	10 ± 4	11 ± 6
Urea (mmol/liter)	5.7 ± 0.8	13 ± 10
Creatinine (μmol/liter)	104 ± 14	189 ± 159
Glucose (mmol/liter)	5.6 ± 0.5	6.2 ± 1.9
Cholesterol (mmol/liter)	6.7 ± 1.1	6.2 ± 0.8
LVEDP (mm Hg)	10.8 ± 4.3	11 ± 3.60
Median time (range) after operation (mo)	—	47 (12–88)
Cyclosporine A level (μg/liter)	—	328 ± 248
Drugs		
Beta-blockers	9	0
Calcium antagonist	10	0
Nitrates	11	0

Unless otherwise indicated, data are expressed as mean value ± SD or number of patients. CAD = coronary artery disease; ESR = erythrocyte sedimentation rate; Hb = hemoglobin; LVEDP = left ventricular end-diastolic pressure; — = not applicable.

Table 2. Systemic Hemodynamic Variables and Coronary Blood Flow Measurements Before and After Esophageal Infusion in Coronary Artery Disease Group

	Before Infusion	After Infusion
Acid infusion		
HR (beats/min)	70 ± 14	73 ± 14
SBP (mm Hg)	135 ± 19	133 ± 17
RPP	9,424 ± 2,035	9,621 ± 2,101
CBF (ml/min)	70.4 ± 14.3	46.4 ± 19.1*
LAD diameter (mm)	4.16 ± 0.38	4.17 ± 0.37
Endothelin-1 (pmol/liter)	3.5 ± 1.3	3.5 ± 1.3
Epinephrine (ng/liter)	64.4 ± 17	66.7 ± 17
Norepinephrine (ng/liter)	327 ± 120	324 ± 126
Saline infusion		
HR (beats/min)	71 ± 12	72 ± 11
SBP (mm Hg)	135 ± 17	133 ± 15
RPP	9,590 ± 1,896	9,642 ± 1,775
CBF (ml/min)	73.5 ± 15.3	72.5 ± 14
LAD diameter (mm)	4.16 ± 0.37	4.17 ± 0.36
Endothelin-1 (pmol/liter)	3.3 ± 1.3	3.3 ± 1.1
Epinephrine (ng/liter)	63.6 ± 23	67.1 ± 18
Norepinephrine (ng/liter)	328 ± 126	330 ± 139

*$p < 0.01$, before versus after infusion, Wilcoxon signed rank test for paired data. Data presented are mean value ± SD. CBF = coronary blood flow; LAD = left anterior descending coronary artery; RPP = rate-pressure product (heart rate [HR] × systolic blood pressure [SBP]).

To obtain an estimate of coronary blood flow at rest (in ml/min), the rest cross-sectional area of the coronary artery (in cm^2) was multiplied by the mean coronary blood flow velocity (in cm/s) and by 60 s.

Statistical analysis. On the basis of results from our previous study (7), it was considered that ≥60% of patients with coronary artery disease would demonstrate a reduction in coronary blood flow with esophageal acid stimulation. The heart transplant group, because of cardiac denervation, was estimated to have <5% incidence of reduction in coronary blood flow with esophageal acid stimulation. The study was planned to have 80% power to detect such a difference between the two groups at alpha 0.05 (two-sided). To achieve this power, 14 patients were needed in each group. Results are given as mean value ± SD. The Wilcoxon signed rank test for paired data was used for statistical evaluation of the data recorded in the coronary flow study. Differences were considered to be significant at the $p < 0.05$ level.

Results

Patient characteristics are shown in Table 1.

Chest pain. Nine (64%) of 14 patients in the coronary artery disease group experienced typical chest pain on esophageal acid stimulation. However, no significant electrocardiographic (ECG) changes were observed in the recorded leads in any patient. None of the patients in the coronary artery disease group reported any chest pain on esophageal saline stimulation.

No patient in the heart transplant group reported any chest pain with either esophageal acid or saline stimulation.

Hemodynamic measurements. There were no significant changes in heart rate, systolic arterial pressure and rate pressure product on esophageal stimulation in both the coronary artery disease group (Table 2) and the heart transplant group (Table 3).

Coronary flow measurements. Esophageal acid stimulation in the coronary artery disease group produced a significant reduction in coronary blood flow from 70.4 ± 14.3 ml/min to 46.4 ± 19.1 ml/min ($p < 0.01$) (Table 2, Fig. 1). However, on esophageal saline stimulation, the coronary blood flow was not affected (Table 2, Fig. 2). In the heart transplant group, the rest coronary blood flow was not affected by both acid and saline infusions (Table 3, Fig. 3 and 4).

Coronary artery disease subgroup analysis. The patients with coronary artery disease who had chest pain on esophageal acid stimulation were then compared with those patients who did not experience typical anginal chest pain. There were no clinical variables predictive of patients experiencing chest pain on acid infusion, and there was no significant difference in the antianginal medications normally taken by the two subgroups.

Chest pain on acid infusion (Table 4). Nine patients experienced typical chest pain on acid infusion. There were no significant differences in systemic hemodynamic conditions.

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Table 3. Systemic Hemodynamic Variables and Coronary Blood Flow Measurements Before and After Esophageal Infusion in Heart Transplant Group

	Before Infusion*	After Infusion*
Acid infusion		
HR (beats/min)	91 ± 7	93 ± 8
SBP (mm Hg)	136 ± 13	137 ± 17
RPP	12,307 ± 1,289	12,643 ± 2,002
CBF (ml/min)	56.3 ± 32	57.4 ± 33
LAD diameter (mm)	3.92 ± 0.14	3.94 ± 0.13
Endothelin-1 (pmol/liter)	3.6 ± 1.2	3.6 ± 1.2
Epinephrine (ng/liter)	68.9 ± 24	70.6 ± 26
Norepinephrine (ng/liter)	311 ± 78	308 ± 78
Saline infusion		
HR (beats/min)	93 ± 7	93 ± 6
SBP (mm Hg)	137 ± 11	135 ± 10
RPP	12,720 ± 1,380	12,480 ± 1,156
CBF (ml/min)	56.3 ± 32	57.4 ± 33
LAD diameter (mm)	3.92 ± 0.13	3.94 ± 0.13
Endothelin-1 (pmol/liter)	3.5 ± 1.1	3.6 ± 0.9
Epinephrine (ng/liter)	68.2 ± 27	68.3 ± 27
Norepinephrine (ng/liter)	312 ± 79	313 ± 77

*p = NS for all comparisons, before versus after infusion, Wilcoxon signed rank test for paired data. Data presented are mean value ± SD. Abbreviations as in Table 2.

The coronary flow decreased from 73.4 ± 12.9 to 34.6 ± 4.7 ($p < 0.01$, Fig. 5).

No chest pain on acid infusion (Table 4). Five patients did not experience any chest pain on acid infusion. There were no significant changes in heart rate, mean arterial pressure, systolic arterial pressure and rate pressure product. The coronary flow also did not change significantly (Fig. 6).

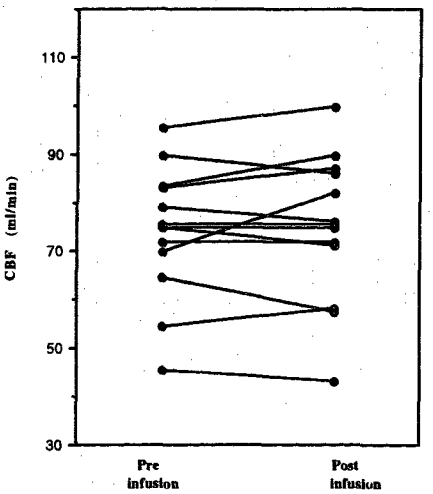


Figure 2. Effect of saline infusion on coronary blood flow (CBF) in patients with coronary artery disease.

Left anterior descending coronary artery diameter. Quantitative measurements did not show a significant difference before and after the esophageal infusions (Tables 2 and 3).

Catecholamine and endothelin levels. There was no significant difference in the levels of epinephrine, norepinephrine and endothelin-1 in the coronary sinus samples before and after the acid and saline infusions in both groups of patients (Tables 2 to 4).

Figure 1. Effect of acid infusion on coronary blood flow (CBF) in patients with coronary artery disease.

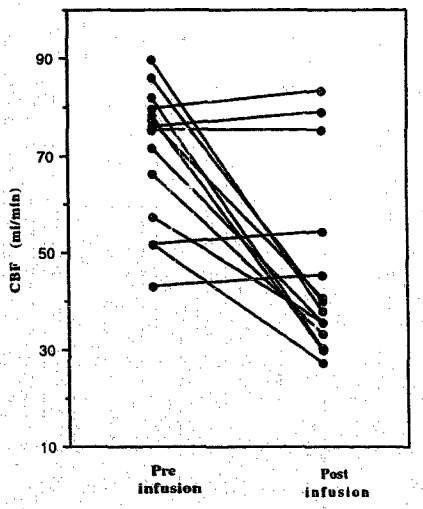
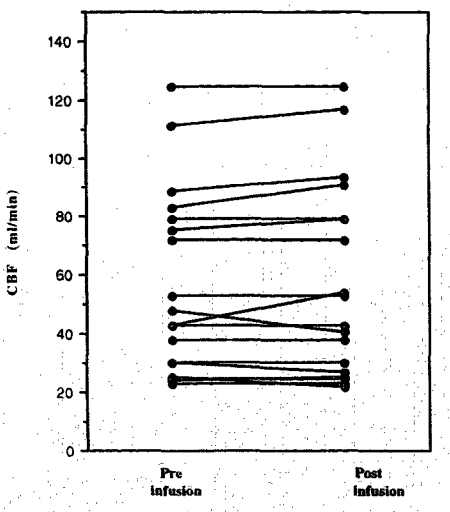


Figure 3. Effect of acid infusion on coronary blood flow (CBF) in heart transplant recipients.



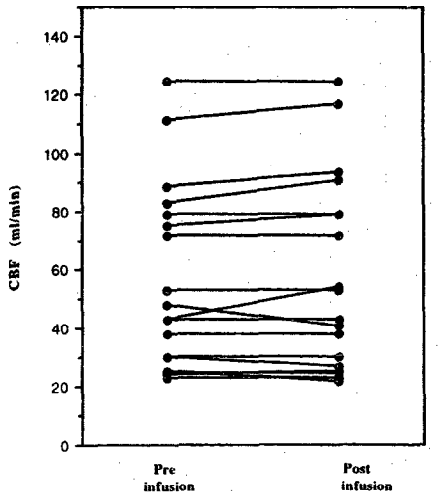


Figure 4. Effect of saline infusion on coronary blood flow (CBF) in heart transplant recipients.

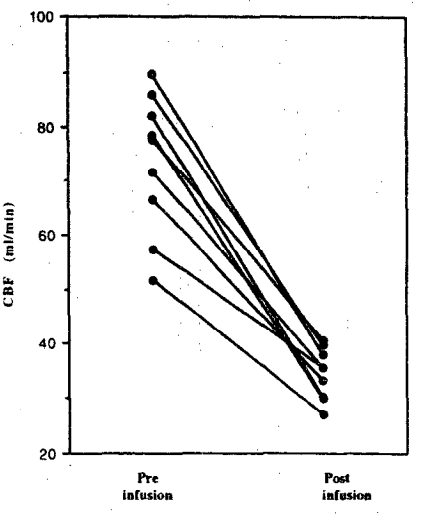


Figure 5. Effect of acid infusion on coronary blood flow (CBF) in patients with coronary artery disease who experienced chest pain on infusion.

Discussion

Study findings. The present study demonstrated that esophageal acid stimulation can reduce coronary blood flow in patients with coronary artery disease. This reduction in coronary blood flow is associated with typical anginal pain, occurs in the absence of any significant change in the epicardial coronary artery diameter and is not associated with any significant changes in the levels of catecholamines and endothelin-1. The coronary blood flow was not affected in the heart transplant group suggesting a neural cardio-esophageal reflex mechanism.

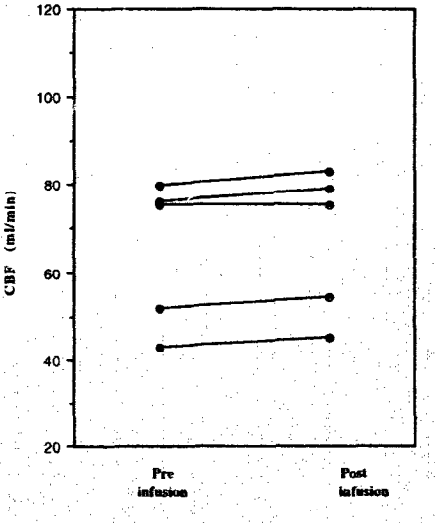
The Doppler technique of subselective coronary blood flow velocity measurements is accurate and has been validated more extensively than any others currently in use (15). Coronary blood flow velocity measurements can be affected by changes in heart rate and arterial pressure (16). However,

Table 4. Coronary Artery Disease Subgroup Analysis

	Before Infusion	After Infusion
Pain on infusion		
HR (beats/min)	72 ± 11	74 ± 11
SBP (mm Hg)	129 ± 20	129 ± 19
RPP	9,321 ± 2,263	9,578 ± 2,090
CBF (ml/min)	73.4 ± 12.9	34.6 ± 4.7*
LAD diameter (mm)	4.13 ± 0.34	4.11 ± 0.30
Endothelin-1 (pmol/liter)	3.6 ± 1.2	3.6 ± 1.2
Epinephrine (ng/liter)	63.6 ± 19	64.8 ± 17
Norepinephrine (ng/liter)	307 ± 108	317 ± 107
No pain on infusion		
HR (beats/min)	68 ± 19	70 ± 21
SBP (mm Hg)	144 ± 13	141 ± 10
RPP	9,611 ± 1,777	9,697 ± 2,336
CBF (ml/min)	65.1 ± 16.7	67.5 ± 16.7
LAD diameter (mm)	4.2 ± 0.47	4.3 ± 0.49
Endothelin-1 (pmol/liter)	3.3 ± 1.4	3.3 ± 1.5
Epinephrine (ng/liter)	65.3 ± 16	69.3 ± 18
Norepinephrine (ng/liter)	340 ± 149	342 ± 152

*$p < 0.01$, before versus after infusion, Wilcoxon signed rank test for paired data. Data presented are mean value ± SD. Abbreviations as in Table 2.

Figure 6. Effect of acid infusion on coronary blood flow (CBF) in patients with coronary artery disease who did not experience chest pain on infusion.



there was no significant effect on the systemic hemodynamic condition as a result of acid or saline infusion in both groups of patients. It is also unlikely that the changes observed in the study were due to natural variations in rest coronary flow velocity as it has been shown previously that there is little variation in the rest coronary flow with time (17).

Possible mechanisms. *Reduction in coronary blood flow.* Nine of the 14 patients with coronary artery disease experienced typical anginal pain on acid infusion, and this was associated with a significant reduction in coronary blood flow. However, saline infusion failed to produce chest pain in any patient and the coronary blood flow was not affected. The observed reduction in coronary blood flow on esophageal acid stimulation occurred in the absence of any changes in the left anterior descending coronary artery diameter, which excludes epicardial coronary artery spasm and which suggests an increase in microvascular resistance.

Increase in microvascular resistance. The increase in microvascular resistance may have been due to release of vasoconstrictor substances, either locally at the level of the coronary microcirculation or systemically. Evidence for inappropriate constriction of the small-diameter distal vessels rather than the proximal large-diameter coronary arteries as a cause of myocardial ischemia is accumulating (18,19). Vasoconstrictor substances such as neuropeptide Y and endothelins have also been identified, which produce ischemia predominantly by small-vessel coronary constriction (20,21). The absence of any hemodynamic changes during the study makes substance release into the systemic circulation as a result of esophageal stimulation unlikely. The absence of any effect on coronary blood flow in the heart transplant group supports the presence of a cardioesophageal reflex that is disrupted in the patients as a result of heart transplantation. It is unlikely that the lack of effect in the heart transplant group can simply be attributed to the absence of coronary artery disease as we have previously demonstrated that esophageal acid stimulation can reduce coronary blood flow in angiographically normal coronary arteries (7). The reflex may either increase the tone of the microcirculation directly or produce the same effect by causing the release of vasoconstrictor substances locally. There was no significant change in the levels of catecholamines or endothelin-1 in the coronary sinus blood samples in both the heart transplant and coronary artery disease groups. Furthermore, there was no significant difference between patients with coronary disease who experienced pain associated with a reduction in coronary blood flow and those who did not. This provides support for the presence of a reflex mechanism causing an increase in microvascular resistance by the release of neurotransmitters rather than substances such as endothelin as a source of the vasoconstriction.

Enhanced vasoconstrictor response. Endothelium-dependent relaxation is impaired in atherosclerotic human coronary arteries and is manifested as paradoxic constriction to vasodilator agonists such as acetylcholine, augmented responses to known vasoconstrictors, impaired flow mediated dilation in conductance arteries and impaired vasodilator function in resistance arteries (22). Disturbances of endothelial function may play an important role in the abnormal vasoconstriction associated with the occurrence of myocardial ischemia in patients with coronary atherosclerosis. Impairment of endothelial-dependent vasodilation with atherosclerosis is simply not confined to advanced and stenotic lesions but has been observed in arteries containing only minor irregularities (23,24) and in completely smooth arteries where atherosclerosis is present elsewhere in the coronary vascular tree (25), suggesting that impaired endothelium-dependent vasodilation occurs early in the course of atherosclerosis. It has been demonstrated, both in vitro in experimental animals (26) and in vivo in humans (27), that endothelial dysfunction accompanying atherosclerosis renders the vessels more sensitive to the constrictor effects of catecholamines. The divergent effects of serotonin on coronary vasomotor tone have also been reported in patients with normal and atherosclerotic coronary arteries (28,29). An enhanced vasoconstrictor response to neurotransmitters released locally in the presence of endothelial dysfunction is, therefore, also a possible mechanism.

Vagal stimulation. The paradoxic vasoconstriction produced by acetylcholine infusion in patients with atherosclerosis also raises the possibility that a similar effect could occur with vagal activation. Because vagal stimulation releases acetylcholine that reaches endothelial receptors and produces vasodilation in healthy vessels (30), it would seem probable that in the diseased atherosclerotic vessel, vagal stimulation might produce vasoconstriction in the presence of endothelial dysfunction. Evidence for an association between esophageal disorders, vagal tone and cardiac effects in support of a cardioesophageal reflex is also provided by several other studies (31–35). Although a parasympathetic coronary vasodilator tone at rest has not been demonstrated in humans, previous studies have suggested that coronary arteries may be constricted by vasomotor nervous impulses transmitted by the vagus nerve. It has been shown in dog experiments that coronary flow may be reduced by distension of the stomach or of the abdominal cavity (36). This reduction in flow does not occur after vagal section or after the administration of atropine, suggesting reflex coronary vasoconstriction initiated by vagal irritation in the gastrointestinal tract. A similar reflex coronary vasoconstriction initiated in the lung (37) and in the heart itself (38) has also been demonstrated.

Our study has demonstrated the occurrence of a neurally mediated microvascular coronary constriction as a result of pain from esophageal stimulation. This is a general sympathetic response to pain of any origin rather than the reflex being unique to the esophagus. However, we have previously shown that esophageal acid stimulation can produce chest pain and reduce coronary blood flow in syndrome X patients, whereas intracardiac stimulation produced typical angina in the absence of any significant changes in coronary blood flow (7,39). This would argue against a general sympathetic response to pain.

There were no significant ECG changes during the esophageal stimulation tests in the cardiac catheter laboratory.

However, only two leads were monitored owing to technical reasons. It may be that the ischemic changes did occur but were missed as a result. Alternatively, the duration of blood flow reduction may not have been of sufficient length to lead to ischemic changes although it was sufficient to produce chest pain. Duration and frequency of esophageal stimulation are important factors in producing changes on the electrocardiogram. This is suggested by our previous observations that ST segment depression occurs only after prolonged or frequent episodes of gastroesophageal reflux and that single, short episodes of reflux may not produce any ST segment changes although the patients experience typical anginal pain (40).

Animal studies have shown that excitatory inputs from stimulation of somatic fields and visceral organs converge onto spinal neurons, including spinothalamic and spinoreticular tract neurons (41–43). This convergence of visceral and somatic inputs provides a neural basis for explaining the referred pain often associated with ischemic heart disease. Garrison et al. (44) have demonstrated that referred pain from the distal esophagus resulted from activation of the same spinal neurons by visceral and somatic input and that the pain originating from the distal esophagus and the heart may be difficult to distinguish because of viscerosomatic and visceravisceral convergence into the same spinal neurons. In the absence of ECG changes of ischemia, the link between the chest pain and the reduced coronary blood flow could be explained in one of two ways: The pain might be caused by the reduced coronary blood flow, or pain originating in the esophagus might activate sympathoexitatory pathways via the spinal cord (a visceral spinal reflex) or higher centers (through spinothalamic tract connections to cardiovascular related nuclei) to cause constriction of the small coronary arteries. It is possible that the chest pain experienced by the patients in our study arises from the esophagus even though a reflex may be elicited that results in a decrease in coronary blood flow. This still demonstrates a novel reflex not previously demonstrated in patients with angiographically proven coronary artery disease. The possibility of the coexistence of esophageal and coronary disease suggests that the presence of this reflex may have important implications.

Study limitations. The coronary blood flow measurements were obtained in the left anterior descending coronary artery that did not have significant stenoses (>30%) so that the measurements of coronary blood flow velocity may not be affected unpredictably. We did not measure blood flow in arteries with significant stenoses; therefore, we can only speculate that this reflex may be active in producing a decrease in coronary blood flow in arteries that already have stenoses. The results of this study are similar to the previous observation in patients with syndrome X that esophageal acid stimulation can reduce coronary blood flow associated with typical anginal chest pain (7). This raises the possibility that a cardioesophageal reflex mechanism is present in normal humans; and this only becomes important in the presence of an impaired coronary flow reserve, endothelial dysfunction or significant coronary stenoses.

There is current evidence for spontaneous reinnervation of the transplanted heart and restoration of sinus arrhythmia and baroreceptor function (45). None of the heart transplant recipients included in the present study had demonstrated sinus arrhythmia on ECG recordings. However, it has been shown recently that the response of the sinus node to stimulatory maneuvers cannot be taken as evidence for or lack of reinnervation of the remainder of the heart as reinnervation after cardiac transplantation is regionally heterogeneous (46). We did not perform tyramine studies in the heart transplant recipients for the presence of reinnervation.

The mechanism of the reflex vasoconstriction needs further investigation as to whether the reflex is central or spinal and whether alpha- or beta-adrenergic blockade can affect the reflex.

Conclusions. The present study demonstrated that esophageal stimulation can reduce coronary blood flow in patients with coronary artery disease, providing support for the previously suggested diagnosis of linked angina. This reduction in coronary blood flow provides further evidence for the presence of a cardioesophageal reflex in humans and may have important implications in patients who have both esophageal and coronary artery disease.

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