17. Nishimura S, Kimball KT, Mahmarian JJ, Verani MS. Angiographic and hemodynamic determinants of myocardial ischemia during adenosine thallium-201 scintigraphy in coronary artery disease. *Circulation* 1993;87:1211–1219.
18. Chambers CE, Brown KA. Dipyridamole induced ST segment depression during thallium 201 imaging in patients with coronary artery disease: angiographic and hemodynamic determinants. *J Am Coll Cardiol* 1988;12:37–41.
19. DeServi S, Ferrario M, Ghio S, Angoli L, Bramucci E, Ardissino D, Specchia G. Effects of atrial pacing and dipyridamole administration on coronary hemodynamics of collateralized myocardial regions in stable angina pectoris. *Am J Cardiol* 1990;65:703–708.
20. Nienaber CA, Salge D, Spielman RP, Montz R, Bleifeld W. Detection of human collateral circulation by vasodilation-thallium-201 tomography. *Am J Cardiol* 1990;65:991–998.

Cardiac Vagal Control and Dynamic Responses to Psychological Stress Among Patients With Coronary Artery Disease

Paul Grossman, PhD, Lana L. Watkins, PhD, Frank H. Wilhelm, PhD, Dimitris Manolakis, PhD, and Bernard Lown, MD

Impaired control of parasympathetic modulation of heart rate has been associated with cardiovascular mortality in patients with coronary artery disease (CAD) and among older populations of indeterminate cardiovascular status.[1,2] Cardiac vagal activity moderates stress-related sympathetic influences upon the heart and blood pressure variations.[3,4] The opposing forces of parasympathetic and sympathetic efferent discharge are important determinants of cardiac stress reactions and influence susceptibility to ventricular arrhythmias in heart disease.[3,5] Because mental stress contributes to risk among CAD patients and because diminished vagal control has been associated with elevated mortality, it is important to delineate the role of cardiac vagal control in mediating cardiovascular reactions to mental stress in CAD. This study examined links between cardiovascular stress responses and individual differences in cardiac parasympathetic control among stable CAD patients. Patients with high and low levels of cardiac vagal activity, as indexed by respiratory sinus arrhythmia (RSA), were compared during a public-speaking mental stressor and at rest. Dependent measures included mean RR interval, blood pressure, rate-pressure product, cardiac output, total peripheral resistance, and baroreflex sensitivity.

• • •

Fifteen patients with highest levels of cardiac vagal control and 15 patients with lowest vagal control were selected from 46 patients with documented CAD. Exclusion criteria were congestive heart failure, malignant ventricular arrhythmias, rheumatic heart disease, hemodynamically significant aortic stenosis or aortic valvular insufficiency, mitral valve disease, ejection fraction <30%, age >75 years, diabetes, body mass index >35 kg/m^2, absence of normal sinus rhythm, >2 previous myocardial infarctions, and the daily use of class 1 and 3 antiarrhythmic agents, or digitalis.

From the Lown Cardiovascular Research Laboratory, Brookline, Massachusetts. Dr. Grossman's address is: Lown Cardiovascular Research Laboratory, 21 Longwood Ave., Brookline, Massachusetts 02146.
Manuscript received April 2, 1996; revised manuscript received and accepted July 9, 1996.

All patients were maintained on their normal medication schedule during the study in order to provide results representative of real-life stress responses of coronary patients. Groups did not differ in type or number of medications. The only significant clinical difference between groups (Table I) was office heart rate, which was higher as expected in the group with reduced vagal activity. There was also a tendency toward more severe coronary occlusion in the low-vagal group. There were no differences between groups on personality measures of depression (Beck Depression Inventory), hostility (Buss–Derkee Scale), or anxiety (Spielberger Trait Anxiety Scale).

Experimental conditions were presented in the morning to seated subjects in the following order: (1) voluntary paced-breathing, via auditory signal, at 9, 12, 15 and 18 cycles/min (3-minute periods), (2) a 10-minute pretask resting baseline, and (3) a 7-minute standard public-speaking task[15] in which patients prepared and presented a speech about an emotionally evocative situation.

The vagal-control classification was determined from mean spectral-analysis-derived RSA during paced breathing to control for the confounding influences of respiratory parameters upon amplitude of RSA.[6] Various studies confirm the high within-subject stability of RSA over time.[7,8]

The following signals were recorded: electrocardiogram, Finapres (Ohmeda, Louisville, Colorado) beat-to-beat finger blood pressure, Respitrace (Ardsley, New York) abdominal and thoracic respiration, and end-tidal carbon dioxide via nasal cannula (Novametrix, Wallingford, Connecticut). Finapres estimates of blood pressure are highly correlated with intraarterial measures.[9,10]

Digitized data were stored on computer. Sampling frequencies were 400 Hz for the electrocardiogram, 200 Hz for blood pressure and CO_2 signals, and 25 Hz for respiration. Physiologic signals were analyzed off-line by computer using customized programs. Suspect cardiac intervals were reviewed using the original electrocardiographic signal as means of verification. Ectopic or other abnormal beats were deleted from the RR interval series and replaced by

TABLE I Characteristics of Low- and High-Vagal Coronary Artery Disease Groups (± SEM)

	Low-Vagal Group (n = 15)	High-Vagal Group (n = 15)
Paced RSA (ms^2)	40.2 ± 1.4	575.7 ± 4.3
Ln RSA (ms^2)	3.4 ± 0.2	6.2 ± 0.2
Age (yr)	62.0 ± 0.8	59.3 ± 0.7
Body mass index	27.4 ± 0.4	28.1 ± 0.5
Office heart rate (beats/min)*	68.1 ± 1.0*	59.5 ± 0.8*
Office blood pressure (mm Hg)	130/78 ± 17/10	124/79 ± 16/10
Left ventricular ejection fraction	67.3 ± 0.8	60.5 ± 0.7
Documented MI	53%	53%
Time since MI (yr)	6.8 ± 0.9	9.1 ± 1.0
Current angina	87%	60%
Catheterization performed	53%	53%
Mean number of occluded coronary arteries (>70%)†	1.8 ± 0.3	1.1 ± 0.3
Bruce protocol exercise duration		
5–9 min	47%	33%
>9 min	53%	67%
Mean maximum exercise ST depression (mm)	1.1 ± 1.2	1.2 ± 1.1

* $p < 0.05$; † $p < 0.10$.
MI = myocardial infarction; ln = natural logarithm; RSA = respiratory sinus arrhythmia

TABLE II Mean Levels (± SEM) of Dependent Measures During Speech Stress and 10-Minute Baseline Preceding Stress

Measure	Low-Vagal X ± SEM		High-Vagal X ± SEM	
Systolic pressure (mm Hg)				
Baseline	138.6	7.4	143.2	6.4
Speech	190.2	8.7	184.5	7.1
Diastolic pressure (mm Hg)				
Baseline	73.7	3.3	74.3	3.4
Speech	100.9	4.6	93.3	3.6
Heart rate (beats/min)				
Baseline	66.8	2.5	53.2	1.6
Speech	78.6	2.9	65.1	2.0
Cardiac output (L/min)				
Baseline	4.5	0.2	4.1	0.3
Speech	4.8	0.2	4.6	0.3
Peripheral resistance (U)				
Baseline	1.3	0.1	1.6	0.2
Speech	1.8	0.2	1.8	0.2
Rate-pressure product				
Baseline	9,123.9	553.3	7,570.5	325.0
Speech	14,515.8	744.0	11,729.8	369.9
Baroreflex gain (ms/mm Hg)				
Baseline	4.2	0.8	6.2	0.5
Speech	3.3	0.6	4.3	0.5
RSA (ln ms^2)				
Baseline	4.1	0.3	6.1	0.1
Speech	3.9	0.3	5.2	0.2

ln = natural logarithm; RSA = respiratory sinus arrhythmia.

linearly interpolated values. Records with greater than 10% ectopic beats were not submitted for spectral analysis.

Mean values per condition were calculated for heart rate, systolic, diastolic blood pressure, and rate-pressure product. Respiratory parameters were analyzed to assure adherence to paced-breathing conditions. Additionally, cardiac output and systemic total peripheral resistance change were determined by the previously validated pulse-contour analysis (BEATFAST, TNO-BMI, Amsterdam, The Netherlands).[11]

RSA and baroreflex sensitivity were estimated by means of power spectral and cross-spectral analysis. Our spectral estimation procedure used the Welch algorithm, which averages periodograms.[12] Time series of beat-to-beat RR intervals were linearly interpolated at a frequency of 4 Hz. For each experimental condition, 60-second segments data, overlapping by half, were then detrended, filtered with a Hanning window, and fast Fourier transformed to provide frequency content. Identical procedures were employed for systolic blood pressure and for respiration. Bandwidths employed were 0.070 to 0.1299 Hz (low-frequency band) and 0.13 to 0.50 Hz (high-frequency, or RSA, band). Previous research has determined that RSA is almost exclusively vagally mediated.[6] Low-frequency RR interval power reflects both vagal and sympathetic modulation and is largely a consequence of baroreflex feedback mechanisms.[13] RR interval spectral data were transformed to natural logarithms in order to normalize distributions.

To estimate baroreflex sensitivity, cross-spectral analysis of the magnitude component of the transfer function employed systolic pressure as input and RR interval as output.[14] Baroreflex sensitivity was the magnitude of RR change per millimeters of mercury within the low-frequency band where the coherence was >0.5. Data not reaching criterion were treated as missing.

Repeated-measures analyses of variance were employed with 1 grouping factor (vagal control) and Greenhouse–Geisser corrections. Whenever baseline levels of a variable differed between groups, analyses of covariance adjusting for baseline values were used to examine stress responses.

All mean data are presented in Table II. Mean heart rate differed between groups across all conditions with higher values for the low-vagal group ($p < 0.0001$). Both groups responded to stress with an

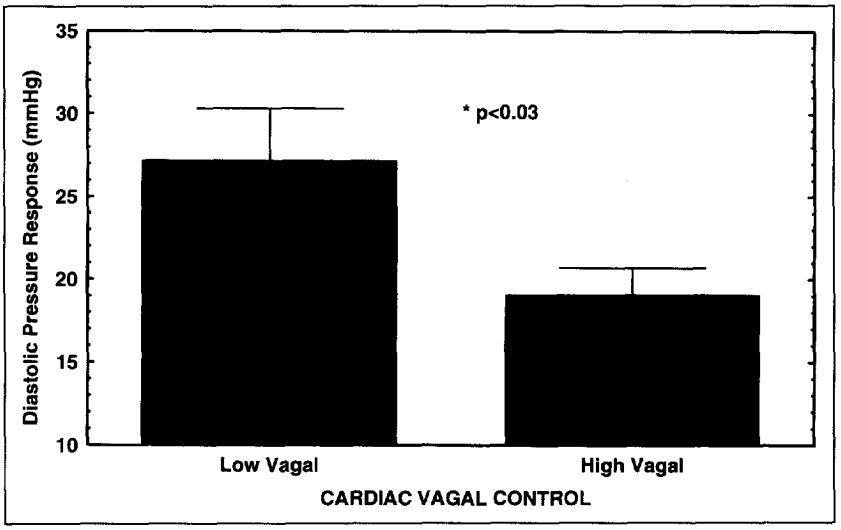

FIGURE 1. Diastolic blood pressure responses during speech stress (mean speech level minus baseline level). The significance level reflects group differences: low-vagal patients showed greater reactions to stress.

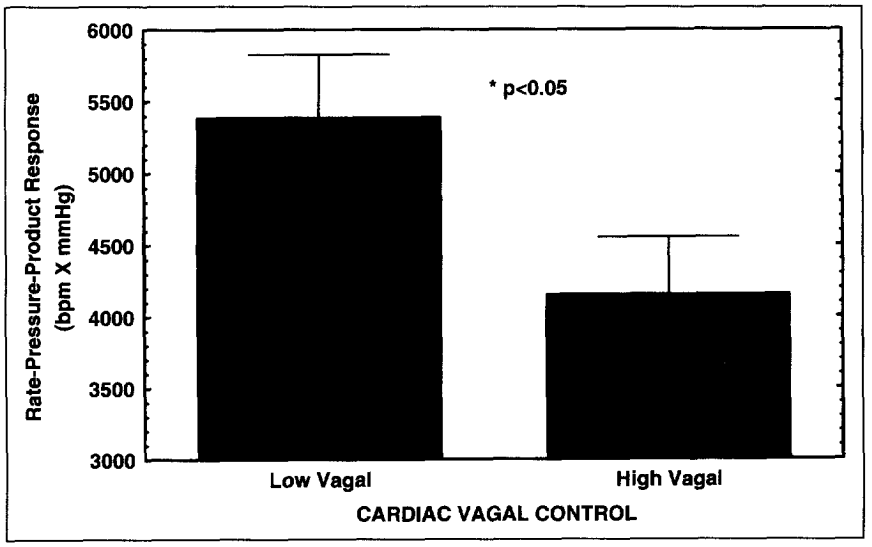

FIGURE 2. Rate-pressure product responses during speech stress (mean speech level minus baseline level). The significance level reflects group differences: low-vagal patients showed higher levels across conditions and greater reactions to stress. Differences between groups remained significant after adjusting for baseline levels.

increase in heart rate ($p < 0.0001$). There were no differences between groups in heart-rate responses to stress, although the heart-rate level of high-vagal patients during stress was approximately the same as the *baseline* level for low-vagal patients.

Systolic and diastolic blood pressures increased from baseline to stress ($p < 0.0001$). There were no group differences in baseline levels of systolic or diastolic blood pressure. However, there was a group X condition interaction for diastolic reactions to stressor tasks (Figure 1): low-vagal patients demonstrated greater diastolic responses to the speech task ($p < 0.03$).

Rate-pressure product was higher among low-vagal subjects and greater during stress as opposed to baseline ($p < 0.003$). A group X condition interaction effect indicated that the low-vagal group displayed greater rate-pressure product increases to mental stress than the high-vagal group (Figure 2; $p < 0.05$). Rate-pressure product reactions to stress remained significant after adjustment for baseline levels ($p < 0.05$). Both rate-pressure product and diastolic reactions were correlated with RSA across all 46 patients of the study ($r = 0.3$, $p < 0.05$), suggesting continuous relations.

Cardiac output increased from rest to stress ($p < 0.001$, respectively). Although there was no group difference, post-hoc *t* tests revealed that only the high-vagal group produced a significant stress-related increase in cardiac output from baseline ($p = 0.03$). Both low- and high-vagal groups increased total peripheral resistance during the speech task ($p < 0.0007$ and $p < 0.01$, respectively). There was also a tendency for the low-vagal group to show a greater increase in total peripheral resistance during the stress task as compared to the high-vagal group ($34.3\% \pm 7.6\%$ vs $15.9\% \pm 5.1\%$; $p = 0.056$).

Baroreflex sensitivity was attenuated for the low-vagal group across all conditions ($p < 0.002$) and diminished across groups from rest to mental stress ($p < 0.0001$).

• • •

The principal findings are that level of parasympathetic cardiac control is associated with cardiovascular and autonomic responses to stress among CAD patients. Diastolic blood-pressure response during speech stress increased among those patients with lower levels of parasympathetic control, confirming a previous report.[16] This was consistent with a tendency among low-vagal patients toward a greater increase in total peripheral resistance, in contrast with high-vagal patients. Increased peripheral resistance will place extra work load on an already compromised myocardium due to increased afterload.

Although there were no differences in systolic pressure, groups varied in levels of rate-pressure product and in stress-induced changes in rate-pressure product, low-vagal patients showing greater increases of rate-pressure product to the speech stressor. Rate-pressure product is an index of myocardial

oxygen demand. These data suggest that low levels of parasympathetic cardiac control may be directly related to elevated myocardial oxygen demand, possibly leading to an elevated risk of ischemia. Indeed, other studies have tied mental-stress-induced ischemia to exaggerated rate-pressure product reactions among patients with CAD.[17,18]

A dulling of dynamic parasympathetic responsiveness among low-vagal patients was suggested by the low level of baroreflex sensitivity in this group. Attenuated baroreflex cardiac-interval responses to phenylephrine have recently been reported as independent predictors of cardiac mortality and reduced threshold to ventricular fibrillation.[19, 20] Baroreflex-mediated cardiac responses are vagally mediated, but apparently reflect a different aspect of vagal reactivity than RSA, since the 2 are only moderately correlated ($r \approx 0.6$) in this and other studies.[21] These data are consistent with the hypothesis that sympathetic dominance at relatively low levels of tonic and baroreflex-mediated vagal control may, owing to lack of vagal restraint, result in excessive pressor and myocardial metabolic demand during psychological stress, as indicated by the exaggerated diastolic-pressure and rate-pressure product reactions among the low-vagal patients.

Certain limitations of these findings should be noted. Because patients were maintained on medications during the study, it was impossible to tease apart the effects of medications and disease. Nevertheless, the 2 groups studied were similar in medication schedule and extent of disease. Given that most CAD patients are medicated, it seemed appropriate to study them in their habitual physiologic state without exposure to possible physiologic and psychological consequences of drug withdrawal. Secondly, all patients in this investigation could be characterized as moderate in the extent of heart disease, and histories usually indicated a stable course of CAD. Relations between cardiac parasympathetic control and cardiovascular adjustments to behavioral stress may be different dependent upon the severity of disorder. Thirdly, we cannot exclude that other mechanisms besides cardiac vagal control may underlie both vagal differences and cardiovascular reactions to stress. Although clinical characteristics of the 2 groups were similar, a tendency toward greater coronary occlusion was observed among low-vagal patients. Nevertheless, much experimental evidence indicates that decreased vagal tone mediates intracellular effects of catecholamines, promotes electrical instability of the myocardium, and may potentiate sympathetic effects upon chronotropic and inotropic heart function.[5] It seems, therefore, likely that variations in cardiac vagal control may moderate stress responses.

This study indicates that variations in cardiac vagal control among coronary patients are related to cardiovascular responses to behavioral stress. With impaired vagal control, repeated demands of everyday life may produce exaggerated pressor and myocardial metabolic states that presage enhanced cardiovascular risk.

1. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation* 1993;88:927–934.
2. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, Levy D. Reduced heart rate variability and mortality risk in an elderly cohort: The Framingham Heart Study. *Circulation* 1994;90:878–883.
3. Verrier RL, Lown B. Experimental studies of psychophysiological factors in sudden cardiac death. *Acta Med Scand Suppl* 1982;660:57–68.
4. Grossman P, Brinkman A, de Vries J. Cardiac autonomic mechanisms associated with borderline hypertension under varying behavioral demands: evidence for attenuated parasympathetic tone but not for enhanced beta-adrenergic activity. *Psychophysiology* 1992;29:698–711.
5. Levy MN, Schwartz PJ, eds. Vagal control of the heart: Experimental basis and clinical implications. Armonk, New York: Futura; 1994.
6. Grossman P, Kollai M. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. *Psychophysiology* 1993;30:486–495.
7. Kleiger RE, Bigger JT, Bosner MS, Chung MK, Cook JR, Rolnitzky LM, Steinman R, Fleiss JL. Stability over time of variables measuring heart rate variability in normal subjects. *Am J Cardiol* 1991;68:626–630.
8. Stein PK, Rich MW, Rottman JN, Kleiger RE. Stability of index of heart rate variability in patients with congestive heart failure. *Am Heart J* 1995;129:975–981.
9. Virolainen J. Use of non-invasive finger blood pressure monitoring in the estimation of aortic pressure at rest and during the Mueller manoeuvre. *Clin Physiol* 1992;12:619–628.
10. Imholz BP, Settels JJ, van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovasc Res* 1990;24:214–221.
11. Stok WJ, Baisch F, Hillebrecht A, Schulz H, Meyer M, Karemaker J. Non-invasive cardiac output measurement by arterial pulse analysis compared with inert gas rebreathing. *J Appl Physiol* 1993;74:2687–2693.
12. Welch PD. The use of fast Fourier transform for the estimation of power spectra: a method based on time averaging over short modified periodograms. *IEEE Trans Audio Electroaccoust* 1967;15:70–73.
13. deBoer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. *Am J Physiol* 1987;253:H680–H689.
14. Watkins L, Grossman P, Sherwood A. Noninvasive assessment of baroreflex control in borderline hypertension: comparison with the phenylephrine method. *Hypertension* 1996;28:238–243.
15. Ironson G, Barr T, Boltwood M, Bartzokis T, Dennis C, Chesney M, Spitzer S, Segall GM. Effects of anger on ventricular ejection fraction in coronary artery disease. *Am J Cardiol* 1992;70:281–285.
16. Jiang W, Hayano J, Coleman ER Hanson MW, Frid DJ, O'Connor C, Thurber D, Waugh R, Blumenthal JA. Relation of cardiovascular responses to mental stress and cardiac vagal activity in coronary artery disease. *Am J Cardiol* 1993;72:551–554.
17. Zotti AM, Bettinardi O, Soffiatino F, Tavazzi L, Steptoe A. Psychophysiological stress testing in postinfarction patients: psychological correlates of cardiovascular arousal and abnormal cardiac responses. *Circulation* 1991;83(suppl 4):II25–II35.
18. Krantz DS, Helmers KF, Bairey CN, Nebel LE, Hedges SM, Rozanski A. Cardiovascular reactivity and mental stress-induced myocardial ischemia in patients with coronary artery disease. *Psychosom Med* 1991;53:1–12.
19. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992;85:I77–I91.
20. Farrell TG, Odemuyiwa O, Bashir Y, Cripps TR, Malik M, Ward DE, Camm AJ. Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. *Br Heart J* 1992;67:129–137.
21. Bigger JTJ, La Rovere MT, Steinman RC, Fleiss JL, Rottman JN, Rolnitzky LM, Schwartz PJ. Comparison of baroreflex sensitivity and heart period variability after myocardial infarction. *J Am Coll Cardiol* 1989;14:1511–1518.