JACC Vol. 31, No. 2
February 1998:301–6

Gender Difference in Autonomic and Hemodynamic Reactions to Abrupt Coronary Occlusion

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Objectives. **We sought to determine whether there are gender-related differences in autonomic and hemodynamic responses to abrupt coronary occlusion.**

Background. **The risk of sudden death before hospital admission is higher in men with an acute myocardial infarction. The reasons for this gender-related difference are not well understood. Cardiovascular autonomic regulation modifies the outcome of acute coronary events, and there are gender differences in the autonomic regulation of heart rate (HR) in normal physiologic circumstances.**

Methods. **We analyzed the changes in HR, HR variability and blood pressure and the occurrence of ventricular ectopic beats during a 2-min coronary occlusion in 140 men and 65 women referred for single-vessel coronary angioplasty. The ranges of nonspecific responses were determined by analyzing a control group of 19 patients with no ischemia during a 2-min balloon inflation in a totally occluded coronary artery.**

Results. **Women more often had ST segment changes ($p < 0.01$) and chest pain ($p < 0.05$) during the occlusion. Significant bradycardia or increase in HR variability as a sign of vagal activation occurred more often in women than in men (31% vs. 13%, $p < 0.01$ and 25% vs. 11%, $p < 0.05$, respectively). Coronary occlusion also more often caused (28% vs. 11%, $p < 0.01$) a decrease in blood pressure in women. The most pronounced female preponderance was in the incidence of Bezold-Jarisch–type reaction (i.e., simultaneous bradycardia and decrease in blood pressure [16% vs. 0.7%, $p < 0.0001$]). Logistic regression models developed to analyze the significance of gender while controlling for baseline variables and signs of ischemia identified female gender to be an independent predictor of bradycardic reactions (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.4 to 7.7, $p < 0.01$), hypotensive reactions (OR 2.6, 95% CI 1.1 to 6.0, $p < 0.05$) and Bezold-Jarisch–type response (OR 22.2, 95% CI 2.5 to 200, $p < 0.01$). Significance of female gender as a protector against early coronary occlusion-induced ventricular ectopic beats emerged as having borderline significance (OR 0.4, CI 0.1 to 1.1, $p = 0.07$).**

Conclusions. **Vagal activation is more common in women than in men during abrupt coronary occlusion and may have beneficial antiarrhythmic effects, modifying the outcome of acute coronary events.**

(J Am Coll Cardiol 1998;31:301–6)

Sudden death, usually occurring within minutes of the onset of chest pain, is the first clinical manifestation of coronary artery disease in as many as 20% to 25% of patients (1). The risk of early sudden death before hospital admission is higher in men than in women with an acute myocardial infarction (2–3), but the reasons for this gender-related difference are not well understood. Abrupt coronary occlusion may cause a wide range of autonomic and hemodynamic reactions, as evidenced by changes in heart rate (HR), blood pressure and HR variability (4–6), and experimental studies have suggested that these autonomic reactions may modify the clinical presentation of acute ischemic events (7–10). A temporal relation between changes in HR variability and life-threatening ventricular tachyarrhythmias has also been demonstrated in patients with coronary artery disease (11,12). Recent research (13–15) has shown that there are gender-related differences in the autonomic modulation of HR. Because there are no clinical data on potential gender-related differences in autonomic responses to abrupt coronary occlusion, we determined to assess these effects in a prospective series of patients undergoing clinically indicated coronary angioplasty.

Methods

Study patients. The study included 140 consecutive men and 65 consecutive women undergoing clinically indicated coronary angioplasty and fulfilling the following criteria: 1) single-vessel coronary angioplasty; 2) stenosis in the proximal or midportion of the vessel, causing >50% reduction in the arterial diameter, with normal anterograde flow (Thrombolysis

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Manuscript received June 3, 1997; revised manuscript received September 23, 1997, accepted October 13, 1997.

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Published by Elsevier Science Inc.

0735-1097/98/$19.00
PII S0735-1097(97)00489-0

Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram, electrocardiographic
HR = heart rate
OR = odds ratio
RMSD = root mean square of differences between successive RR intervals
TIMI = Thrombolysis in Myocardial Infarction

in Myocardial Infarction [TIMI] grade 3 flow) (16); 3) myocardial ischemia documented with exercise electrocardiography or perfusion scan; 4) no or minimal wall motion abnormality in the myocardial territory at risk; 5) sinus rhythm and no bundle branch block; 6) no acute procedural complications; 7) informed consent of the patient.

A control group of 19 patients (12 men, 7 women) who were treated for a chronic total occlusion (TIMI grade 0 or 1 flow) of a coronary artery were assessed to evaluate the nonspecific changes in HR, blood pressure and HR variability during a 2-min balloon inflation of the occluded artery.

Study protocol. The design was approved by the ethical committee of each institution, and all patients gave their informed consent. Coronary angioplasty was performed by the usual technique (6). Diazepam (5 to 10 mg) was given before the procedure as a tranquilizer. Sublingual nitroglycerin was given before the guiding catheter was placed in the coronary ostium and every 15 min thereafter. No patient was given atropine. In tight coronary artery stenoses, the deflated balloon, or even the guide wire, may compromise blood flow in the vessel, so that observations made before and during the first balloon inflation may be inconsistent and unreliable (17). Thus, an initial short balloon angioplasty (≤20 s) was performed as soon as possible after introduction of the balloon into the stenosis. A normal coronary flow was ascertained with a contrast medium injection after this predilation. The balloon inflation to be used for data acquisition was performed after 5 min for recovery. The occlusion was designed to last up to 120 s, but the occlusion was relieved earlier if it caused intolerable chest pain; hemodynamic instability; or multiform, bigeminal or repetitive ventricular premature beats. No contrast medium was injected during data acquisition, and every effort was made to keep the patients unaware of the timing of the balloon inflations and to maintain the circumstances as stable as possible to minimize the effects of nonspecific distress on HR or blood pressure. The patients were accustomed to breathing at a constant rate of ~0.25 Hz from the beginning of the catheterization and were advised to avoid unnecessary talking, especially just before or during data acquisition. In cases of intolerable chest pain during this phase of the procedure, the patients were advised to give a hand signal, and the balloon was deflated. The intensity of chest pain during balloon inflation was assessed on the Borg numeric scale from 1 to 10 immediately after balloon deflation (18). The precordial lead that provided the largest R wave deflection was chosen for on-line electrocardiographic (ECG) monitoring.

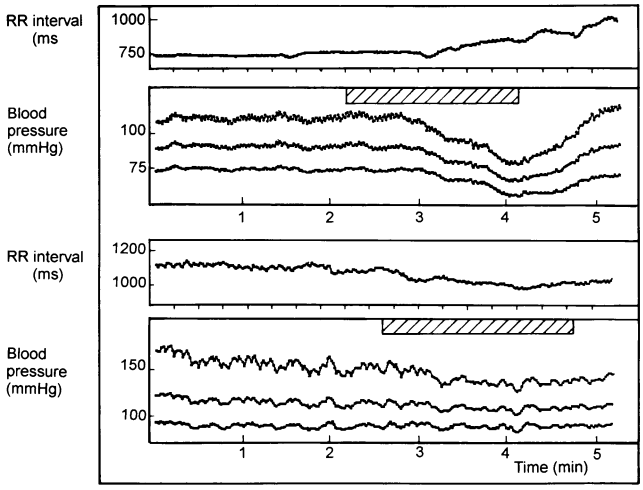

Figure 1. Computer output of beat to beat RR intervals and invasive blood pressure, showing a typical example of Bezold-Jarisch–type vasovagal activation as evidenced by progressive bradycardia and fall in blood pressure during balloon occlusion of a 56% stenosis in the left anterior descending coronary artery in a 50-year old female patient (**upper panels**). An example of an opposite HR reaction (mild tachycardia) during the occlusion of an 84% stenosis in the left circumflex coronary artery seen in a 54-year old man (**lower panels**). The baseline data were analyzed as the mean values over 1-min periods preceding the occlusions and the occlusion data from 1-min periods at the end of the occlusions.

Coronary anatomy. Coronary angiography in at least four projections with cranial and caudal angulated views was performed before angioplasty. The view with the best visualization of the lesion was selected, and the severity of the coronary artery stenosis was measured using the stenosis diameter program included in the Philips DCI S System. The presence of collateral flow was graded according to Cohen and Rentrop (19).

Ventricular ectopic beats. After visual inspection of RR interval tachograms, all ECG recordings were scanned by an experienced observer (K.E.J.A.). Ventricular extrasystoles were identified on the basis of the prematurity and width of the QRS complex (20).

HR and blood pressure data acquisition and analysis. Continuous HR and blood pressure recordings were made immediately before and during the first 2-min balloon inflation (Fig. 1). All data acquisition and analysis were performed by a method previously described in detail using a menu-driven software package (CAFTS, Medikro Oy, Kuopio, Finland) (9,10). The RR intervals were collected from the surface ECG, and arterial pressure was measured from the femoral artery by means of external transducers. The signals were stored in the memory of an IBM PC/AT compatible microcomputer, using an analog-to-digital converter (200 Hz, 12 bits). Regions with no ectopic beats were selected for analysis of HR, HR variability and blood pressure. The baseline data were analyzed from a period of 60 s just before the occlusion, and a similar

region at the end of the balloon occlusion (i.e., starting after 1-min occlusion) was selected for occlusion data. The root mean square of the differences between successive RR intervals (RMSD) was calculated using standard equations.

Definitions of HR and blood pressure reactions. The mean change ±2 SD in HR and systolic blood pressure during a 2-min balloon inflation in a totally occluded vessel in the control group was taken as the normal range of short-term nonspecific fluctuation in these measures. The change in RMSD had to exceed the ±2 SD range in both logarithmic and absolute units to be considered an abnormal change in HR variability. All reactions were considered severe when the changes were outside the mean change ±4 SD range in the control group. The *Bezold-Jarisch reaction* was defined as simultaneous abnormal bradycardia and hypotension (Fig. 1).

Statistical analysis. All analyses were performed using the SPSS for Windows, Release 6.0. The paired *t* test was used for intragroup comparison of the changes in HR and blood pressure. Because the distributions of the measures of HR variability were skewed to the right, nonparametic tests were used for these analyses. Categoric variables for men and women were compared using the chi-square test and the Fisher exact test, and the *t* test was used for comparison of continuous variables. To assess the effect of gender on the incidence of coronary occlusion-induced reactions, logistic regression models were constructed. In the first model, the baseline variables (Table 1) were considered for inclusion as predictor variables, whereas the specified reaction served as the dependent variable. Backward selection was used to delete predictor variables that were not statistically significant ($p > 0.10$), and gender was then added to each basic model. In the second model, the ischemic responses (severity of chest pain and occurrence of ST segment changes) were added to the list of predictor variables. Results for each model are expressed as the odds ratio (OR) of an ischemic reaction in women relative to men, with 95% confidence interval [CI].

Results

Control group. Balloon inflation (duration 120 s) in the preexisting chronic total occlusion of the coronary artery was asymptomatic and did not cause ST segment changes, ventricular ectopic beats or significant changes in mean systolic blood pressure (+3.0 ± 5.6 mm Hg [mean ± SD]), HR (+0.3 ± 2.0 beats/min) or RMSD (−0.2 ± 3.0 ms) in the 19 patients studied.

Clinical characteristics by gender. The clinical characteristics of the study patients by gender are described in Table 1. Women were older than men and were more often hypertensive but less often had a history of myocardial infarction. The occluded coronary artery stenosis was milder in women, but there was no gender difference in the site of occlusion (inferior vs. anterior) or presence of visible collateral vessels. Eight women were taking hormone replacement therapy at the time of the study, and five others had had an earlier postmenopausal estrogen treatment.

Table 1. Clinical and Angiographic Characteristics of Women and Men Undergoing Coronary Occlusion

	Women (n = 65)	Men (n = 140)	p Value
Age (yr)	58 ± 9	54 ± 9	< 0.01
Hx of MI	9 (14%)	40 (29%)	< 0.05
Hypertension	19 (29%)	24 (17%)	< 0.05
Hx of chest pain (mo)	32 ± 47	24 ± 28	NS
Diabetes	5 (8%)	5 (4%)	NS
Beta-blocker	39 (60%)	89 (64%)	NS
Calcium antagonist	27 (42%)	67 (48%)	NS
LVEF (%)	72 ± 14	71 ± 13	NS
Stenosis severity (%)	78 ± 12	82 ± 11	< 0.05
Occluded artery			
LAD	41 (63%)	80 (57%)	NS
LCx	8 (12%)	33 (24%)	NS
RCA	16 (25%)	27 (19%)	NS
Visible collat vessels	10 (15%)	29 (21%)	NS
Occlusion time (s)	108 ± 20	112 ± 20	NS
HR (beats/min)	72 ± 15	70 ± 12	NS
SBP (mm Hg)*	155 ± 31	147 ± 25	NS
DBP (mm Hg)*	83 ± 18	85 ± 12	NS
RMSD (ms)	12 ± 8	11 ± 8	NS
SD of RR intervals (ms)	19 ± 12	18 ± 12	NS

*Data for only 134 men and 64 women because of technical failure in systolic (SBP) and diastolic blood pressure (DBP) recordings in 6 men and 1 woman. Data presented are mean value ± SD or number (%) of patients. Collat = collateral; HR = heart rate; Hx = history; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; RCA = right coronary artery; RMSD = root mean square of successive RR interval differences.

Signs of myocardial ischemia by gender. There was no gender difference in mean coronary occlusion time, but the occlusion had to be stopped prematurely more often in women (23 women [35%] vs. 26 men [19%], $p < 0.01$). Women had ST segment changes more often and had more frequent and more severe chest pain during occlusion (Table 2).

Ventricular ectopic beats by gender. Coronary occlusion was associated with ventricular premature beats in 5 women (8%) and 18 men (13%) (Table 2). When adjusted for baseline variables and signs of ischemia, the OR of ventricular ectopic beats for women versus men emerged as being of borderline significance (OR 0.4, 95% CI 0.1 to 1.1, $p = 0.07$) (Table 3).

HR reactions by gender. There were no significant differences in HR and HR variability at baseline. However, during coronary occlusion, both indexes of HR variability—RMSD and SD of RR intervals—were, higher in women than men (19 ± 23 vs. 12 ± 10 ms and 37 ± 36 vs. 25 ± 18 ms, respectively, $p < 0.05$ for both). Mean HR changes were not significant in either group. When the individual HR reactions were compared with those in the control group, significant bradycardia occurred more often in women than in men (Table 2). The difference was mostly due to the more common occurrence of severe bradycardia (22% vs. 5%, $p < 0.001$). When controlled for baseline variables and signs of ischemia, female gender remained a significant predictor of bradycardic reactions (OR 3.2, 95% CI 1.4 to 7.7, $p < 0.01$) (Table 3).

Table 2. Signs of Ischemia, Ventricular Ectopic Beats and Abnormal Reactions* in Heart Rate, Systolic Blood Pressure and Heart Rate Variability During Balloon Occlusion of Coronary Artery Stenosis by Gender

	Women (n = 65)	Men (n = 140)	p Value
Chest pain	49 (75%)	83 (59%)	< 0.05
Severity†	3.1 ± 2.3	2.4 ± 2.1	< 0.05
ST seg changes	42 (65%)	59 (42%)	< 0.01
Bradycardia	20 (31%)	18 (13%)	< 0.01
Severe	14 (22%)	7 (5%)	< 0.001
B-J reaction‡	10 (16%)	1 (0.7%)	< 0.0001
Tachycardia	12 (19%)	13 (9%)	NS
Severe	5 (8%)	2 (1%)	< 0.05
HR variability§			
Increase	16 (25%)	16 (11%)	< 0.05
Decrease	5 (8%)	7 (5%)	NS
Hypotension‡	18 (28%)	15 (11%)	< 0.01
Severe	10 (17%)	6 (4%)	< 0.01
VEBs‖	5 (8%)	18 (13%)	NS

*See Methods (Definitions). †Borg scale (18) of severity of pain: 1 to 10. ‡Data for only 134 men and 64 women because of technical failure in blood pressure recordings in 6 men and 1 woman, of whom 1 man and 1 woman had significant heart rate (HR) reactions. §Data for only 139 men and 64 women because of extrasystoles during the occlusion data, which made the analysis unreliable in two cases. ‖Data for only 125 men and 60 women (15 men and 5 women with at least one ventricular ectopic beat [VEB] in the baseline period were excluded). Data presented are mean value ± SD. B-J = Bezold-Jarisch; seg = segment.

Coronary occlusion-induced tachycardia tended to be more common in women, but the gender difference was not significant after controlling for baseline variables and signs of ischemia (OR 1.7, 95% CI 0.7 to 4.5, p = 0.24). Significant increases in HR variability were more common in women (25% vs. 11%, p < 0.05), but this difference was not significant after adjustment for significant covariates (OR 2.0, 95% CI 0.9 to 4.6, p = 0.09).

Blood pressure reactions by gender. Baseline systolic blood pressure was higher in women (Table 1). Mean changes in systolic blood pressure were not significant in either group.

Table 3. Crude and Adjusted Odds Ratios With 95% Confidence Intervals for Coronary Occlusion-Induced Reactions in Women Versus Men Estimated From Logistic Regression Models*

	Crude OR (95% CI)	Adjusted OR (95% CI)	
		Model 1	Model 2
Bradycardia	3.0 (1.5–6.2)	3.8 (1.6–8.9)	3.2 (1.4–7.7)
Inc in RMSD	2.6 (1.2–5.5)	1.8 (0.8–4.1)	2.0 (0.9–4.5)
Tachycardia	2.2 (1.0–5.2)	1.6 (0.6–4.0)	1.7 (0.7–4.5)
Hypotension	3.1 (1.4–6.7)	2.6 (1.1–6.1)	2.6 (1.1–6.0)
B-J reaction	24.6 (3.1–200)	25.6 (2.6–254)	22.2 (2.5–200)
VEBs	0.5 (0.2–1.5)	0.4 (0.2–1.3)	0.4 (0.1–1.1)

*In model 1, all baseline variables in Table 1 were considered for adjustment; model 2 was also adjusted for chest pain and ST segment changes. B-J = Bezold-Jarisch; CI = confidence interval; Inc = increase; OR = odds ratio; RMSD = root mean square of successive RR interval differences; VEBs = ventricular ectopic beats.

Hypotensive reactions were more common in women (p < 0.01) (Table 2) and were more often associated with significant HR reactions (14 of 18 vs. 5 of 15, p = 0.01). Female gender remained a significant predictor of hypotensive reactions when controlled for baseline variables and signs of ischemia (OR 2.6, 95% CI 1.1 to 6.0, p < 0.05). The most pronounced gender-related difference was in the occurrence of Bezold-Jarisch–type reactions (Fig. 1), which were observed in 10 women (16%) but only in one man (0.7%, p < 0.0001). The adjusted OR of the Bezold-Jarisch reaction for women versus men was 22.2 (95% CI 2.5 to 200, p < 0.01).

Other predictors. Logistic regression models developed to analyze the significance of gender while controlling for baseline variables indicated that high HR (p < 0.001), low systolic blood pressure (p < 0.01) and inferior site of coronary occlusion (p < 0.05) were the only other baseline variables that were predictive of bradycardic response during coronary occlusion. Absence of beta-adrenergic blocking agent treatment (p < 0.05) was the only independent predictor of significant coronary occlusion-induced increase in HR variability. High systolic blood pressure and high RMSD were predictive of tachycardic (p < 0.001 and p < 0.01, respectively) and hypotensive reactions (p < 0.05 and p < 0.01, respectively). Absence of beta-blocker treatment, old age, diabetes mellitus, low systolic blood pressure and mild stenosis severity were significant predictors of Bezold-Jarisch–type reactions (p < 0.05 for all). Mild stenosis severity (p < 0.05) and left anterior descending coronary artery occlusion (p = 0.06) predicted ventricular ectopic beats during coronary occlusion.

Discussion

Ischemia-induced HR and blood pressure reactions. The present study shows that there are distinct gender-related differences in the HR reactions during abrupt coronary occlusion. The most pronounced difference was the more common occurrence of bradycardic reactions in women, and this gender difference remained significant after adjustments for differences in baseline variables and signs of myocardial ischemia during the occlusion (Table 3). In experimental models, hypotension is a common phenomenon, even during the early stages of acute coronary occlusion (21,22). The present study shows that there are also gender-related differences in blood pressure reactions to abrupt coronary occlusion: Blood pressure decreased in 28% of women but only in 11% men during the early stage of occlusion. Most of this difference was due to the preponderance of Bezold-Jarisch–type reactions in women, characterized by simultaneous bradycardia and hypotension (adjusted OR for women vs. men 22.2, 95% CI 2.5 to 200). The present findings are in agreement with preliminary experimental data (23) suggesting that there is an early significant fall in HR and mean arterial pressure in female rats after coronary artery ligation. In male rats, coronary occlusion caused tachycardia and a less severe fall in arterial pressure. Vagotomy in rats changed the hemodynamic responses of females to a "male" pattern.

Ischemia-induced ventricular arrhythmias. Acute extensive myocardial ischemia often results in malignant arrhythmias due both to direct effects of ischemia as well as the resultant hemodynamic compromise (20,24,25). The first period of ventricular premature complexes, which usually herald malignant ventricular arrhythmias during abrupt coronary occlusion, develop after a quiescent period of 1.5 to 2.5 min and reach a peak at 5 min (26,27). In an experimental model, male gender seems to be an independent predictor of the incidence of ventricular fibrillation during abrupt coronary occlusion (21). In the present study, male gender was of borderline significance in the prediction of early coronary occlusion-induced ventricular ectopic beats (Table 3).

Background for gender differences in HR and blood pressure reactions. During abrupt coronary occlusion, the major afferent input to the autonomic control of the heart comes from the ischemic myocardium (28). Previous experimental studies (29,30) have shown that myocardial ischemia may excite both vagal and sympathetic afferent fibers of cardiac origin. Excitation of cardiac receptors with nonmyelinated vagal afferents distributed mainly in the subendocardial layers leads to an increase in parasympathetic efferent activity and may activate the Bezold-Jarisch reflex (29,31). In contrast, excitation of sympathetic afferent endings closer to the epicardial surface seems to inhibit the activity of efferent vagal fibers (31,32). Thus, the balance between sympathetic and vagal afferent activation may be crucial for the intensity and direction of autonomic reactions. Activation of baroreflexes may also modify the HR reactions.

Previous reports on healthy subjects indicate that there are gender differences in the autonomic regulation of HR in normal physiologic circumstances. Women have a higher HR and lower baroreflex sensitivity, and their HR variability is characterized by a preponderance of high frequency compared with low frequency fluctuations (13–15). Experimental studies (33–35) have suggested that estrogen inhibits the release of norepinephrine in the heart and potentiates cholinomuscarinic activity in the heart and central nervous system under both normal and ischemic conditions. Similar modulation of autonomic activity could contribute to the predisposition of female patients to ischemia-induced vagal efferent activation, although most of the female patients were postmenopausal. Increased stimulation of cardiac vagal afferents may also inhibit the arterial baroreflex and even override the arterial baroreceptor reflex, resulting in vasodilation and increased cardiac vagal efferent activity despite a reduction in arterial blood pressure (28,36,37). Gender-related differences in baroreflex sensitivity and intravascular volume may also contribute to the occurrence of hypotensive reactions (14,15). Previous myocardial infarction may cause autonomic denervation apical to the site of infarction (38). Although women less often had a history of myocardial infarction, this difference is unlikely to explain our findings because only patients with minimal or no wall motion abnormalities were included, and none of the occlusion-induced reactions were related to a history of myocardial infarction.

Study limitations. Balloon occlusion of a coronary artery is a widely used model for controlled myocardial ischemia. For ethical reasons, the occlusion time was limited here to a maximum of 2 min, which gives the opportunity to assess only the initial occlusion-induced reactions. Furthermore, coronary occlusion was discontinued after the appearance of hemodynamic instability or bigeminal or repetitive premature beats, and so the risk of malignant hemodynamic reactions or ventricular arrhythmias could not be evaluated. With regard to sympathetic activation, many intrinsic mechanisms inhibit the accumulation of norepinephrine in the myocardium within the first few minutes of ischemia (39). Thus, the present findings may not be directly applicable to more prolonged periods of coronary occlusion and myocardial ischemia. Although logistic regression analysis was used to determine the independent effect of gender on various coronary occlusion-induced reactions, we cannot exclude the possibility that some unknown or unmeasured covariate of gender may have contributed to the observed gender differences.

Clinical implications. Our results show that women more often have signs of vagal activation during abrupt coronary occlusion. Vagal activation may have both beneficial and harmful clinical consequences. Experimental studies (7–10) have shown that augmented parasympathetic activity has protective and antifibrillatory effects during acute myocardial ischemia. These antiarrhythmic effects may protect women against early out of hospital sudden death during acute myocardial infarction and contribute to the observed gender difference in the clinical presentation of acute myocardial infarction (2,3). This concept is also supported by experimental data (21) suggesting that female gender protects against ventricular arrhythmias during abrupt coronary occlusion. However, there are also data (40,41) to suggest that extreme vagal activation may lead to cardiac asystole or hemodynamic instability. In this respect there seems to be a female preponderance in middle-aged patients with unexplained or vasodepressor syncope and fatal bradyarrhythmias (42,43). Predisposition to hypotensive and severe bradycardic reactions may also contribute to the greater prevalence of shock and syncope in women during the acute phase of myocardial infarction and to the higher risk for fatal acute complications of coronary angioplasty in women (44,45).

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