Editorial Comment

Unraveling the Mechanisms of Ambulatory Ischemia

How and Why

Peter H. Stone, MD

Since the early description of the phenomenon of transient asymptomatic ischemia during ambulatory ECG monitoring in patients with stable coronary disease, there has been considerable interest as to whether these episodes are due to increases in myocardial O_2 demand, to decreases in myocardial O_2 supply as a result of coronary vasoconstriction, or to some variable combination of the two. The issue is important not only to understand the pathophysiology of this phenomenon but also to guide the selection of effective anti-ischemia medication.

Mechanisms of Ambulatory Ischemia

Heart rate has been the only hemodynamic variable available from ambulatory ECG monitoring to indicate whether a particular episode of ischemia is due to an increase in myocardial O_2 demand (i.e., an increase in heart rate preceding ST segment depression) or, by default, to a decrease in myocardial O_2 supply (i.e., no preceding increase in heart rate). Conflicting observations of heart rate activity preceding episodes of ischemia have stirred a debate concerning pathophysiologic mechanisms: some investigators report that a majority of episodes are preceded by an increase in heart rate,[1,2] whereas others report that a majority are not preceded by an

See p 1296

increase in heart rate.[3,4] A consistent finding among all investigators, however, is that the heart rate at the onset of ischemia during outpatient activities, assessed by ambulatory ECG monitoring, is lower than the heart rate at the onset of ischemia during a supervised exercise test,[3,5,6] suggesting that episodic coronary vasoconstriction lowers the ischemic threshold during outpatient activities and is at least partially responsible for episodes of ambulatory ischemia.

Assessment of pathophysiologic mechanisms based on heart rate activity alone, however, can obviously be misleading because other major hemodynamic variables, such as afterload (blood pressure), preload, and contractility, also determine myocardial O_2 demand. The inadequacy of using heart rate alone to reflect the nature of the pathophysiologic disturbance is underscored by the fact that although the correlation between heart rate and blood pressure changes throughout an ambulatory monitoring period are generally good,[7] the sympathetic response to various activities such as mental stress,[8–10] isometric exercise,[10,11] cigarette smoking,[12] and exposure to cold[13] may become manifest as a predominant increase in blood pressure and a lesser increase in heart rate. The presence of hypertension[7] and even the process of aging[7] are associated with exaggerated blood pressure responses to stress compared with heart rate responses. In this issue of *Circulation*, Deedwania and Nelson[14] provide important confirmation of the pathophysiology of ambulatory ischemia and demonstrate by concomitant heart rate and blood pressure monitoring that the majority of ischemic episodes are preceded by increases in both heart rate and blood pressure.

The other important contribution from Deedwania and Nelson's report[14] is the confirmation that a substantial number of ischemic episodes occur *without* an increase in the determinants of myocardial O_2 demand and presumably, therefore, occur from coronary vasoconstriction. The processes of fixed obstructive coronary atherosclerosis and episodic coronary vasoconstriction are closely linked in coronary disease, most likely due to the development of endothelial dysfunction and consequent loss of endothelium-dependent dilatation associated with the development of atherosclerosis.[15] In some patients, paradoxical coronary vasoconstriction occurs in response to a variety of normal daily activities that are associated with increased sympathetic activity. If the vasoconstrictive response to a sympathetic stimulus predominates, an episode of ischemia may appear to arise "spontaneously," without a major rise in the determinants of myocardial O_2 demand. Dynamic or isometric exercise, for example, is associated with a 35–71% reduction in coronary

The opinions expressed in this editorial comment are not necessarily those of the editors or of the American Heart Association.

From Harvard Medical School and the Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Mass.

Address for reprints: Peter H. Stone, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

luminal area in patients with coronary disease.[16,17] Similarly, mental stress,[18] cigarette smoking,[19] and exposure to cold,[20] each of which may variably increase heart rate and blood pressure, are also associated with a marked decrease in coronary luminal diameter and the precipitation of myocardial ischemia. Even an increase in heart rate alone, due to atrial pacing, has been associated with a reduction in coronary luminal area of up to 73% compared with a control value in patients with severe coronary disease.[21] Thus, although the majority of episodes of ambulatory ischemia are due to an increase in heart rate and blood pressure, sympathetic activation may also lead to coronary vasoconstriction and, consequently, episodes of ischemia without a major increase in myocardial O_2 demand.

Selection of Anti-Ischemia Therapy Based on the Responsible Mechanism

Since increased sympathetic activity may lead both to increases in heart rate and/or blood pressure and to coronary vasoconstriction, a distinction between episodes based on these different mechanisms may be somewhat artificial or arbitrary. Results from recent pharmacologic studies, however, indicate that such a distinction is valuable when selecting optimal treatment. The efficacy of medications to prevent episodes of ambulatory ischemia has not been uniform and, in general, has paralleled the respective heart rate reduction obtained with each form of therapy. β-Adrenergic blockers have consistently and significantly reduced episodes of ambulatory ischemia,[22] although β-blockers with intrinsic sympathomimetic activity and lack of heart rate reduction are less effective than β-blockers without that property.[23] The importance of heart rate reduction in the treatment of ambulatory ischemia is underscored by a recent report[24] that directly compared propranolol, diltiazem, and nifedipine in patients with stable angina and found that the efficacy of each agent to reduce ischemic episodes paralleled the respective drug-induced reduction in heart rate. Propranolol was associated with a marked decrease in the frequency and severity of ambulatory ischemia as well as a marked decrease in the heart rate. Diltiazem reduced the frequency of ambulatory ischemia, but significantly less than propranolol, and also reduced the heart rate significantly less than the β-blocker. The short-acting formulation of nifedipine increased the heart rate compared with placebo and had no significant effect on episodes of ischemia.[24] It appears that although episodic vasoconstriction may contribute to the occurrence of ambulatory ischemia, therapies directed primarily at that mechanism are not effective unless accompanied by a reduction in sympathetically mediated phenomena such as heart rate and, presumably, myocardial O_2 demand.

Even effective therapies that reduce myocardial O_2 demand, like the β-blockers, only *reduce* episodes of ambulatory ischemia; they do not eliminate them. The episodes of ischemia that remain despite β-blockade may represent those due mainly to coronary vasoconstriction and may be best treated by agents such as the calcium blockers or nitrates. Assuming that it is beneficial to eliminate all episodes of ambulatory ischemia, it will be important for future research efforts to identify various specific daily activities associated with ambulatory ischemia which may be due to marked coronary vasoconstriction. Mental stress, for example, is a frequent stimulus for the development of ambulatory ischemia,[25] yet the specific pathophysiologic response to mental stress that should be the target for treatment is controversial. Mental stress–induced ischemia may be due to excessive coronary vasoconstriction[18,26] or may be due to an exaggerated heart rate and blood pressure response that is displayed by some individuals with a more generalized heightened adrenergic response to stress.[27] Careful drug studies with various therapeutic regimens and careful attention to heart rate and blood pressure patterns will be of great value.

The circadian pattern of ischemic episodes is also important. Coronary vascular tone is increased in the morning[28] and may be responsible for the observation that an increase in heart rate in the morning is more likely to result in ischemia than a similar heart rate rise in the afternoon and evening.[6] Some studies indicate that episodes of ischemia that persist despite β-blockade may have a peak incidence in the morning,[29] while others suggest that β-blockade abolishes the morning peak of ambulatory ischemia, with the peak incidence of remaining episodes occurring in the evening.[30] It will be necessary to evaluate heart rate/blood pressure patterns in episodes persisting despite β-blockade to determine whether they represent an increase in myocardial O_2 demand not adequately blocked or represent episodic vasoconstriction that would not be treated by a β-blocker. The therapeutic justification for identifying heart rate activity preceding ambulatory ischemia is reinforced by a recent preliminary report which suggested that β-blockers effectively reduced ischemic episodes occurring at moderate and high heart rates, whereas nitrate therapy reduced only episodes occurring at low heart rates.[31]

The phenomenon of ambulatory asymptomatic ischemia in patients with stable coronary disease has attracted a vast amount of clinical and investigative interest, and Deedwania and Nelson[14] have provided an important step to elucidate its pathophysiology. It must be emphasized that these research efforts are all predicated on the hypothesis that episodes of asymptomatic ischemia are of independent prognostic significance and warrant specific therapy, a hypothesis that is currently being tested. If this hypothesis is proven to be correct, the efforts of investigators exploring the process of asymptomatic ischemia and its optimal treatment may be translated into an improved outcome for the many patients with stable coronary disease who manifest episodes of asymptomatic ischemia.

Acknowledgment

I am grateful to Mary Gillan for help in preparation of the manuscript.

References

1. Quyyumi AA, Wright CA, Mockus LJ, Fox KM: Mechanisms of nocturnal angina pectoris: Importance of increased myocardial oxygen demand in patients with severe coronary artery disease. *Lancet* 1984;1:1207–1209
2. Quyyumi AA, Efthimiou J, Quyyumi A, Mockus LJ, Spiro SG, Fox KM: Nocturnal angina: Precipitating factors in patients with coronary artery disease and those with variant angina. *Br Heart J* 1986;56:346–352
3. Deanfield JE, Selwyn AP, Chierchia S, Maseri A, Ribeiro P, Krikler S, Morgan M: Myocardial ischemia during daily life in patients with stable angina: Its relation to symptoms and heart rate changes. *Lancet* 1983;2:753–758
4. Chierchia S, Gallina A, Smith G, Deanfield J, Morgan M, Croom M, Maseri A: Role of heart rate in the pathophysiology of chronic stable angina. *Lancet* 1984;2:1353–1357
5. Cecchi AC, Dovellini EV, Marchi F, Pucci P, Santoro GM, Fazzini PF: Silent myocardial ischemia during ambulatory electrocardiographic monitoring in patients with effort angina. *J Am Coll Cardiol* 1983;1:934–939
6. Rocco MB, Barry J, Campbell S, Nabel E, Cook EF, Goldman L, Selwyn AP: Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* 1987;75:395–400
7. Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, Grassi G, diRienzo M, Pedotti A, Zanchetti A: Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983;53:96–104
8. Deanfield JE, Kensett M, Wilson RA, Shea M, Horlock P, deLandsheere CM, Selwyn AP: Silent myocardial ischemia due to mental stress. *Lancet* 1984;2:1001–1004
9. Rozanski A, Bairey CN, Krantz DS, Friedman J, Resser KJ, Morrell M, Hilton-Chalfen S, Hestrin L, Bietendorf J, Berman DS: Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. *N Engl J Med* 1988;318:1005–1012
10. Fredrikson M, Danielssons T, Engel BT, Frisk-Holmberg M, Strom G, Sundin O: Autonomic nervous system function and essential hypertension: Individual response specificity with and without beta-adrenergic blockade. *Psychophysiology* 1985; 22:167–174
11. Grossman E, Oren S, Garavaglia GE, Schmeider R, Messerli FH: Disparate hemodynamic and sympathoadrenergic responses to isometric and mental stress in essential hypertension. *Am J Cardiol* 1989;64:42–44
12. Deanfield JE, Shea MJ, Wilson RA, Horlock P, deLandsheere CM, Selwyn AP: Direct effects of smoking on the heart: Silent ischemic disturbances of coronary flow. *Am J Cardiol* 1988; 57:1005–1009
13. Raizner AE, Chahine RA, Ishimori T, Verani MS, Zacca N, Jamal N, Miller RR, Luchi RJ: Provocation of coronary artery spasm by the cold pressor test. Hemodynamic, arteriographic and quantitative angiographic observations. *Circulation* 1980; 62:925–932
14. Deedwania PC, Nelson JR: Pathophysiology of silent myocardial ischemia during daily life: Hemodynamic evaluation by simultaneous electrocardiographic and blood pressure monitoring. *Circulation* 1990;82:1296–1304
15. Harrison DG, Freiman PC, Armstrong ML, Marcus ML, Heistad DD: Alterations of vascular reactivity in atherosclerosis. *Circ Res* 1987;61(suppl II):II-74–II-80
16. Brown BG, Lee AB, Bolson EL, Dodge HT: Reflex constriction of significant coronary stenosis as a mechanism contributing to ischemic left ventricular dysfunction during isometric exercise. *Circulation* 1984;70:18–24
17. Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Krayenbuehl HP: Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: Reversibility by nitroglycerin. *Circulation* 1986; 73:865–876
18. Yeung AC, Vekshtein VI, Vita JA, Fish RD, Krantz DS, Ganz P, Selwyn AP: Vasomotor response of coronary arteries to mental stress (abstract). *Circulation* 1989;80(suppl II):II-591
19. Maouad J, Fernandez F, Barrillon A, Gerbaux A, Gay J: Diffuse or segmental narrowing (spasm) of the coronary artery during smoking demonstrated on angiography. *Am J Cardiol* 1984;53:354–355
20. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP: Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. *Circulation* 1988;77:43–52
21. Nabel EG, Selwyn AP, Ganz P: Paradoxical narrowing of atherosclerotic coronary arteries induced by increases in heart rate. *Circulation* 1990;81:850–859
22. Stone PH: Mechanisms of silent myocardial ischemia: Implications for selection of optimal therapy. *Adv Cardiol* 1990; 328–348
23. Quyyumi AA: Effect of partial agonist activity in beta blockers in severe angina pectoris. *Br Med J* 1984;289:951–953
24. Stone PH, Gibson RS, Glasser SP, DeWood MA, Parker JD, Kawanishi DT, Crawford MH, Messineo FC, Shook TL, Raby K, Curtis DG, Hoop RS, Young PM, Braunwald E, and the ASIS Study Group: Comparison of propranolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina: Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms. *Circulation* (in press)
25. Barry J, Selwyn AP, Nabel EG, Rocco MB, Mead K, Campbell S, Rebeca G: Frequency of ST-segment depression produced by mental stress in stable angina pectoris from coronary artery disease. *Am J Cardiol* 1988;61:989–993
26. Verrier RL, Hagested EL, Lown B: Delayed myocardial ischemia induced by anger. *Circulation* 1987;75:249–254
27. Specchia G, deServi S, Falcone C, Gravazzi A, Angoli L, Bramucci E, Ardissino D, Mussini A: Mental arithmetic stress testing in patients with coronary artery disease. *Am Heart J* 1984;108:56–63
28. Fugita M, Franklin D: Diurnal changes in coronary blood flow in conscious dogs. *Circulation* 1987;76:488–491
29. Willich SN, Pohjola-Sintonen S, Bhatia SJS, Shook TL, Tofler GH, Muller JE, Curtis DG, Williams GH, Stone PH: Suppression of silent ischemia by metoprolol without alteration of morning increase of platelet aggregability in patients with stable coronary artery disease. *Circulation* 1989;79:557–565
30. Mulcahy D, Cunningham D, Crean P, Wright C, Keegan J, Quyyumi A, Fox K: Circadian variation of total ischemic burden and its alteration with anti-anginal agents. *Lancet* 1988;2:755–759
31. McLenachan JM, Weidinger EF, Barry J, Selwyn AP: Relationships between heart rate, ischemia and drug therapy during daily life in patients with coronary artery disease (abstract). *J Am Coll Cardiol* 1990;15:107A

(*Circulation* 1990;82:1528–1530)