Increased Demand Versus Reduced Supply and the Circadian Variations in Ambulatory Myocardial Ischemia

Therapeutic Implications

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Although it is now widely accepted that silent myocardial ischemia detected by ambulatory ECG monitoring (AEM) is the most common form of ischemia, the debate regarding the pathophysiological mechanisms responsible for ischemic episodes during daily life is far from being settled. Because most of the early investigations in this field had reported that the vast majority of transient ischemic episodes (TIEs) occurred during periods of little or no physical activity, it generally was assumed that mechanisms other than an increase in myocardial oxygen demand might be responsible in their genesis. Although most patients in the earlier investigations had evidence of obstructive lesions secondary to coronary atherosclerosis as well as ischemia secondary to increased oxygen demand during exercise testing, based on relatively lower heart rates during TIEs recorded by AEM, it was suggested that coronary vasoconstriction might play a role in ischemia during daily life.

Direct evidence was provided, however, to prove this postulate. It was largely supported by indirect evidence from comparison of heart rates obtained during exercise-induced ischemia versus those evaluated during TIEs recorded by AEM. Subsequent studies have, however, demonstrated that such differences might have been secondary to the progressive and rapid increases in work load during exercise testing, which are clearly in contrast to the gradual increases in myocardial oxygen demand that are associated with ischemia during daily life. Using heart rate as a surrogate for myocardial oxygen demand, recent studies have shown an excellent correlation between exercise ischemic threshold measured during gradual increases in work load and the ischemic threshold at which TIEs are observed during AEM. In addition, it has been suggested that differences in basal heart rate and blood pressure values might account for variations in ischemic threshold measured in different settings. As illustrated in a recent study, this can be avoided by comparing the percent changes instead of absolute values of the parameters evaluated. Such comparisons of changes in heart rate and systolic blood pressure did reveal that both heart rate and blood pressure increased significantly preceding the majority of ischemic episodes during daily life.

Two recent reports in Circulation provide further evidence supporting the role of increased demand. The report by Andrews and colleagues in this issue of Circulation provides strong evidence in support of the role of increased oxygen demand in the genesis of spontaneous ischemia during daily life. This report demonstrates the importance of careful analysis of heart rate changes for prolonged periods preceding and following ischemic episodes recorded during AEM. Through close scrutiny of heart rate changes preceding onset of ST segment depression, these investigators were able to delineate three separate types of ischemic episodes. Not only did this scheme of classification provide insight into the pathophysiological processes involved, but it also allowed the evaluation of different therapeutic responses observed during treatment with various anti-ischemic drugs.

Increased Oxygen Demand Plays a Dominant Role in Ambulatory Ischemia

A careful analysis of continuous minute-by-minute heart rate changes evaluated by Andrews and colleagues showed that 81% of ischemic episodes recorded during daily life are preceded by an increase in heart rate of 5 or more beats per minute. Although several previous studies had provided similar data showing a dominant role of increased heart rate in the genesis of TIEs recorded during AEM, the study by Andrews and colleagues provides additional insight into the mechanisms involved. These investigators have shown that the likelihood of developing ischemia during daily life is directly related to the magnitude and the duration of heart rate increase during the monitoring period. The chance of developing an ischemic episode was quite low when heart rate increment was less than 10 beats per minute and lasted less than 10 minutes. In contrast, there was a great (60%) likelihood of developing an ischemic episode when heart rate increased by 20 beats per minute or more and persisted for 40 minutes or more. The independent predictive value of the magnitude and duration of heart rate increase was confirmed by the multivariate analysis. These findings have obvious clinical implications. Although relatively little information is currently available regarding the impact of various physical and mental stressors encoun-

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tered during daily life on the magnitude and duration of heart rate and blood pressure changes, clearly more research is needed in this area to further elucidate the mechanism of ischemia during daily life.

The subclassification of demand-related ischemic episodes into two distinct categories (type 1 and type 2) also has potential pathophysiological implications. Although it is obvious that the episodes (type 1) that occur during periods of heart rate increase are largely related to increased oxygen demand, the mechanism responsible in the genesis of type 2 episodes is less clear. It is conceivable that type 2 episodes occur due to an interplay of several mechanisms. For example, it is possible that the increase in heart rate observed 0 to 10 minutes preceding these episodes triggers paradoxical narrowing of the stenotic segment and causes vasospasm.12,13 Such paradoxical vasoconstriction can then lead to critical reductions in coronary blood flow during periods of increased oxygen demand and precipitate an ischemic episode. Although such a mechanism emphasizes the role of vasospasm in the genesis of type 2 ischemic episodes, the therapeutic approach might not be different than that effective in suppressing type 1 episodes. Because the initial trigger for type 2 episodes appears to be an increase in heart rate, therapeutic regimen effective in preventing heart rate increase will be equally effective in controlling type 1 and type 2 episodes. This viewpoint is well substantiated by the data reported by Andrews and colleagues11 showing comparable efficacy of propranolol in reducing type 1 and type 2 ischemic episodes. It should also be noted that although both type 2 and type 3 (nondemand related) episodes can occur in many patients with stable atherosclerotic coronary artery disease, all of these patients usually experience type 1 ischemic episodes, which account for the vast majority of ischemia during daily life.

A major limitation of the study by Andrews and colleagues11 as well as the report by Benhorin and coworkers10 is that their evaluations solely relied on heart rate changes as a surrogate for myocardial oxygen demand. Other important determinants of oxygen demand such as blood pressure and myocardial contractility were not evaluated. Because certain daily life situations such as periods of mental stress or exposure to cold are largely associated with changes in blood pressure with varying degrees of heart rate increment, it is crucial to evaluate changes in blood pressure in concert with heart rate changes.14,15 In a previous report,9 we had demonstrated by simultaneous ambulatory blood pressure and ECG monitoring that the vast majority of ischemic episodes during daily life are preceded by an increase in heart rate, systolic blood pressure, or both. Overall, the results of several recent studies7-11 conducting systematic evaluations of changes in heart rate and blood pressure provide overwhelming evidence for a dominant role of increased myocardial oxygen demand in the genesis of spontaneous ischemia during daily life. These findings should not be entirely surprising since it has been known for years that in most patients anginal episodes occur largely due to increased oxygen demand. Although silent ischemic episodes account for most ischemia during daily life, it seemed counterintuitive to think that the pathophysiological process involved would be different for silent than for painful episodes of myocardial ischemia.

**Does Reduced Blood Supply Play a Role in Ischemia During Daily Life?**

Although it is apparent that most ischemic episodes during daily life are related to increased oxygen demand, it is important to emphasize that, albeit small, a primary reduction in coronary blood flow does play a role in some cases. This is largely due to coronary vasospasm, which can occur in nonatherosclerotic segments of coronary artery but usually affects the segment already damaged by the atherosclerotic process.12,13 It is known that coronary atherosclerosis is associated with endothelial dysfunction,13,16 and in some cases sympathetic activation predominantly causes coronary vasoconstriction without necessarily causing a significant increase in demand. Although no direct evidence is available, the type 3 episodes observed by Andrews and colleagues11 must have been largely caused by coronary vasoconstriction because no significant increase in heart rate preceded these episodes. It was interesting to note that the type 3 episodes clustered in seven patients who manifested 47% of such episodes. Although not described in the article,11 it is conceivable that these patients had more advanced and severe distal coronary artery disease, which can be associated with a greater degree of endothelial dysfunction. Based on available data,9-11 it can be concluded that between 20% and 30% of ischemic episodes during daily life might be primarily caused by enhanced coronary vasomotor tone and would be best treated by coronary vasodilating drugs.

**Circadian Pattern of Ambulatory Ischemia and the Related Pathophysiological Process**

Similar to the circadian pattern of acute myocardial infarction17 and sudden cardiac death,18 ambulatory myocardial ischemia9-11 also has bimodal distribution with a peak between 6:00 AM and noon. In the study by Andrews and colleagues,11 both type 1 and type 2 episodes exhibited a circadian distribution with a peak between 6:00 and 9:00 AM. In contrast, the type 3 episodes did not display this circadian pattern and tended to cluster between midnight and 6:00 AM. Also, in the report by Benhorin and colleagues,10 a typical bimodal distribution of ischemic episode was reported with a prominent peak between 7:00 and 11:00 AM and a secondary peak between 6:00 and 9:00 PM.

The increased risk of myocardial ischemia in the morning hours might be related to one or more of the physiological changes observed during this period. These changes include increased heart rate and blood pressure, increased catecholamine levels, heightened coronary vasomotor tone, increased platelet aggregation, and decreased intrinsic fibrinolytic activity.19,20 We had reported that the increase in ischemic episodes during the morning hours closely parallels the increase in heart rate and systolic blood pressure and the calculated double product, emphasizing the role of increased oxygen demand for the circadian pattern of myocardial ischemia. In the study by Andrews and colleagues,11 there also is a close parallel circadian pattern of periods of increased heart rate and ischemic episodes. However, a similar circadian pattern is also observed for periods of increased heart rate that are not associated with
ischemia. The multivariate analysis performed to delineate the importance of time of day revealed that the magnitude and duration of heart rate increment as well as the baseline heart rate had the greatest influence on the likelihood of developing ischemia without a significant independent effect of the time of day.

In their report, Benhorin and colleagues also made some interesting observations. Despite the bimodal distribution of ischemic episodes in their study, these investigators described a single peak in circadian pattern of ischemic threshold that was highest between 10:00 AM and 1:00 PM and lowest between 1:00 and 3:00 AM. Using various statistical analytical methods evaluating the degree of heart rate changes, these investigators also concluded that the morning increase in ischemic episodes is largely attributed to an increase in oxygen demand rather than reduced ischemic threshold. By cross-correlation between the time series of ischemic episodes and ischemic threshold, these investigators were able to demonstrate that both the frequency of ischemic episodes and ischemic threshold might be modified by such common factors as mental arousal, postural changes, and physical activities at a given point in time. These findings are similar to those reported by Andrews and colleagues and emphasize the importance of heart rate changes rather than time of day for the circadian pattern of ischemia. Because of the dominant role of increased oxygen demand, it is not surprising that β-blockers are most effective in suppressing the circadian pattern of myocardial ischemia, and this effect is largely due to their heart rate–lowering action.

Therapeutic Implications

The results of these studies evaluating the pathophysiological processes involved in the genesis of spontaneous ischemia during daily life have significant clinical implications. Based on the above discussion, it seems clear that the ideal therapeutic agent for treatment of spontaneous ischemia during daily life would be a drug that works primarily by lowering the heart rate at rest and also controls the degree of heart rate increment during periods of daily life activities. β-Blockers appear to be best suited to perform such a task. The data reported by Andrews and colleagues clearly demonstrate the efficacy of propranolol in suppressing most type 1 and type 2 ischemic episodes. The effects of propranolol in their study was directly related to its effect on baseline heart rate as well as its ability in preventing long periods of heart rate increment of significant magnitude. Although less efficacious than propranolol, the beneficial effect of diltiazem also appeared to be largely due to its effects on heart rate. The anti-ischemic efficacy of diltiazem has also been demonstrated by Theroux and coworkers in a study of patients with stable CAD, a positive treadmill exercise test, and asymptomatic TIEs on AEM. Both the frequency and duration of TIEs were decreased significantly. Interestingly, in that study the efficacy of diltiazem also correlated well with its effects on heart rate, and there was no circadian variation in the efficacy of diltiazem. In contrast, when the ischemic episodes were not associated with heart rate increase (type 3 episodes), treatment with nifedipine provided the most beneficial effect. This observation is also equally important because between 20% and 30% of ischemic episodes are not demand related and would be best treated by coronary vasodilators. Because some patients might have both demand-related as well as supply-dependent ischemic episodes, combination therapy with an agent that controls heart rate and a coronary vasodilator may be needed to adequately suppress spontaneous ischemia during daily life. The anti-ischemic efficacy of such a combination was recently demonstrated in a study by Parmley and coworkers. In that study, treatment with nifedipine Gastro-Intestinal Therapeutic System (GITS) was effective in attenuating the circadian pattern of myocardial ischemia in patients who continued to have ischemia despite β-blocker therapy. In summary, the results of all these studies underscore the importance of a clear understanding of the pathophysiological processes involved while selecting the most appropriate anti-ischemic therapy in patients with myocardial ischemia.

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Oxygen Demand and Supply and Circadian Variations


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