Circadian variations in total ischaemic burden and ischaemic threshold

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Myocardial ischaemia in daily life varies according to a circadian rhythm and is induced by many factors, including both increased myocardial oxygen demand and changes in coronary tone. In most patients, ischaemia is induced by a combination of different contributing factors, although the relative contribution of each mechanism varies from patient to patient. Moreover, in the same individual, various episodes may be due to different mechanisms. The relative contributions of increased myocardial oxygen demand and decreased ischaemic threshold to the development of ischaemia in daily life can be assessed by continuous ambulatory ECG monitoring which may help to optimize medical anti-ischaemic therapy.

Key Words: Ischaemic heart disease, circadian rhythms, continuous ambulatory ECG Monitoring.

Introduction

Several biological phenomena that may affect the human cardiovascular system exhibit a circadian rhythm, among them plasma cortisol levels which reach a peak at the time of wakening and plasma catecholamine levels which increase during the early morning hours. This heightened sympathetic activity may affect heart rate, blood pressure, cardiac output and cardiac contractility, which all increase in the early morning hours. Increases in haematocrit and blood viscosity have also been reported, along with a morning increase in platelet aggregability and a reduction in fibrinolytic activity. Coronary tone has also been found to be increased in the early morning hours in a study of 21 conscious dogs. In these dogs, the coronary blood flow in the afternoon was 12-8% higher than in the morning. These and other activities subject to circadian rhythms, either alone or in combination, may affect the major determinants of myocardial oxygen demand, coronary tone and myocardial contractility and may contribute significantly to the occurrence of various clinical syndromes and major cardiac events.

Circadian variation of ischaemia

Myocardial ischaemia during daily life, recorded by continuous ambulatory ECG (Holter) monitoring, occurs under multiple conditions including rest, exercise, mental stress, smoking and many other activities. These ischaemic episodes, which were first described by our group in 1973, are mostly silent and occur throughout the day and night. Several investigators have demonstrated that the ischaemic episodes are not evenly distributed during the day but exhibit a distinct circadian rhythm. For example, Rocco and co-workers studied 32 patients with proven coronary artery disease (CAD) and positive treadmill stress tests. Twenty-four of these patients exhibited 251 ischaemic episodes during daily life with 39% of episodes and 46% of ischaemic time occurring between 0600 h and midday. In this study the authors did not observe an increase in heart rate prior to the development of the ischaemic episodes. Mulcahy and coworkers found a circadian pattern of myocardial ischaemia in 150 patients. The total ischaemic burden (silent and painful ischaemia) was maximal in the morning with a trough after midday. In this study the authors did not observe an increase in heart rate prior to the development of the ischaemic episodes. Mulcahy and coworkers found a circadian pattern of myocardial ischaemia in 150 patients. The total ischaemic burden (silent and painful ischaemia) was maximal in the morning with a trough after midday. These authors described a second, less prominent, peak of ischaemic episodes in the late afternoon–early evening, falling off at late evening and night. However, in their study, the heart rate was found to be higher at the time of the maximal frequency of ischaemic episodes. In our study in which 1371 ischaemic episodes were recorded in 41 patients with CAD who underwent 7 days of continuous monitoring, two well-defined peaks of occurrence of ischaemic episodes were observed (Fig. 1). There was a significant increase in the number of ischaemic episodes between 0700 and 1100 h. A second peak, which was not as prominent, was observed between 1700 and 2100 h, whereas the lowest
number of ischaemic episodes was observed at night between 0200 and 0500 h. Hausmann et al. performed a meticulous correlation between the occurrence of ischaemic episodes and changes in heart rate. Their series of 111 patients with chronic stable angina, all with positive exercise tests, had 101 symptomatic and 298 asymptomatic ischaemic episodes. They found that the morning and afternoon increase in the frequency of occurrence of ischaemic episodes was paralleled by a similar circadian variation in heart rate. They did not find evidence for a decrease in myocardial oxygen supply and therefore concluded that the main mechanism leading to daily occurring ischaemic episodes was increased oxygen demand.

Mechanisms of ischaemia in daily life

Understanding the mechanisms responsible for daily ischaemia is of paramount importance as it may require a different therapeutic approach from exercise-induced ischaemia. All researchers who deal with daily ischaemic episodes have noted that these episodes occur at a lower heart rate than that observed during stress testing. In our study of 210 patients, the ischaemic changes during daily activity developed at a mean heart rate of 94 beats.min⁻¹, which was significantly lower than that observed at the onset of ischaemia during exercise testing (109 beats.min⁻¹). Thus, there is no doubt that the daily ischaemia is not only due to increased myocardial oxygen demand, as during exercise testing, but that other mechanisms are involved in its development as well.

In an attempt to understand the mechanism of daily ischaemic episodes more clearly, Andrews et al. performed 48 h of continuous monitoring in 50 patients with proven ischaemic heart disease, positive exercise tests and evidence of daily ischaemic episodes. The ischaemic episodes were divided into three categories: those occurring during a period of increased heart rate (type 1), those occurring 0–10 min after a period of increased heart rate (type 2) and those occurring without increases in heart rate (type 3). The authors found that in 81% of the episodes there was an increase in heart rate and the likelihood of a patient developing ischaemia was strongly correlated with the magnitude of increased heart rate. There was a 4% likelihood of developing ischaemia after a heart rate increase of 5–9 beats.min⁻¹ whereas there was a 60% likelihood of developing ischaemia after an increase in heart rate ≥ 20 beats.min⁻¹. The likelihood of developing ischaemia was also higher in patients with longer duration of heart rate increase. The authors found that a bimodal circadian distribution of types 1 and 2 of ischaemic episodes occurred but there was an even distribution of type 3 episodes throughout the day. Therefore, it was concluded that determinants of myocardial oxygen demand are responsible for most ambulatory ischaemia.

The ischaemic threshold is the workload at onset of ischaemia and can be used as an indirect marker for the severity of coronary disease. Patients who develop ischaemic changes at a low workload probably have more advanced disease than patients with a higher ischaemic threshold. During exercise testing the rate-pressure product at 1 mm of ST depression can be used as the ischaemic threshold, while during daily activities, when the patient’s ECG is being continuously recorded, the heart rate at 1 mm ST depression can be used as the ischaemic threshold. During repeated exercise testing ST depression usually develops in an individual patient at similar heart rates. The presence of a constant and reproducible myocardial ischaemic threshold can be explained by a fixed coronary stenosis which prevents an increase in blood flow during exertion. Thus, exercise-induced ischaemia is caused primarily by an increase in oxygen demand and, therefore, any treatment that will prevent the patient from reaching his own exercise ischaemic threshold will prevent the development of ischaemia.

During daily life ischaemic changes usually develop at a lower heart rate than during exercise. Patients in whom episodes of ST depression develop at a lower heart rate probably have more advanced disease than those in whom ischaemia develops at a faster heart rate. However, ischaemia may develop in the same individual at different heart rates. The dynamic changes in ischaemic threshold have been investigated in a group of 80 patients, all with proven CAD, positive stress tests and who had ≥ 2 ischaemic episodes per 24 h of continuous monitoring and who experienced a total of 895 ischaemic episodes. For each patient we determined the ischaemic threshold of each episode and we defined the lowest heart rate at which ischaemia developed (lowest ischaemic threshold) and the highest heart rate at onset of ischaemia (highest ischaemic threshold). The variability of the ischaemic threshold was defined as the
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mic threshold was present, most episodes were preceded
by a modest increase in heart rate which was not as
increases in the coronary tone, leading to reduced cor-
ary arteries. It was assumed that the presence
of an ischaemic threshold that was significantly lower
than the exercise threshold could best be explained by
increases in the coronary tone, leading to reduced cor-
ary flow in areas with significant stenosis. Even in
patients in whom significant variability in their ischae-
mic threshold was present, most episodes were preceded
by a modest increase in heart rate which was not as
marked as during exercise testing. While in some
patients the variability in ischaemic threshold was as
high as 60\%, it was minimal or absent in others. We
believe that in patients with marked variability in their
ischaemic threshold, dynamic changes in the coronary
tone play a major role in the occurrence of daily ischaemic episodes. Such patients might benefit from
vasodilator therapy with nitrates and calcium channel
blockers, while those with no or minimal variability in
their ischaemic threshold might benefit from \(\beta\)-blockers.
However, since significant variability in ischaemic
threshold was observed in most patients and in most episodes there was also an increase in heart rate, most patients will probably require a combination of \(\beta\)-blockers and vasodilators. Continuous monitoring can help in defining the relative contributions of increased demand and increased coronary tone and may, in the future, help us to identify the most appropriate drugs for individual patients.

Based on the assumption that changes in ischae-
mic threshold are an indirect reflection of coronary tone, we decided to assess whether the ischaemic threshold is subject to a circadian rhythm that might relate to the frequency of occurrence of ischaemic episodes. For this purpose we studied 41 patients with proven CAD who had 1371 ischaemic episodes\(^{\text{[14]}}\). As mentioned earlier, all of these patients had evidence of ischaemia both on the treadmill and on continuous monitoring; 23 patients were not receiving any anti-ischaemic medications, while 18 were on low doses of \(\beta\)-blockers. While the occurrence of ischaemic episodes exhibited a bimodal circadian distribution, the threshold of myocardial ischaemia exhibited a different single peaked circadian distribution (Fig. 1). It was lowest between 0100 and 0300h and highest between 1000 and 1300h. Thus, during the time of maximal occurrence of ischaemic episodes, the threshold of ischaemia was high. The low threshold at night probably reflected an increase of coronary tone during these hours. Accordingly, the increase in frequency of ischaemic episodes during the morning could not be attributed mainly to increased coronary tone and reduced coronary flow but, rather, to an increase in myocardial oxygen demand associated with an increase in heart rate.

Variations in ischaemic thresholds have been reported by other investigators. For example, Figueras and coworkers\(^{\text{[20]}}\) performed repeated atrial pacings in patients with angina at rest and found that the ischaemic threshold during pacing-induced ischaemia was lowest at night. Yasue and coworkers\(^{\text{[21]}}\) performed treadmill exercise tests in 13 patients with Printzmetal's angina in the early morning and in the afternoon of the same day. The attacks of ST elevation were induced repeatedly in all 13 patients in the early morning but in only two patients in the afternoon. In our study\(^{\text{[14]}}\) the 18 patients who received low-dose \(\beta\)-blockers had a lower frequency of ischaemic episodes compared with the 23 patients without anti-ischaemic medication. In the latter group the bimodal circadian distribution of the occurrence of ischaemic episodes was maintained, however, their ischaemic threshold remained constant throughout the day. Since it was assumed that changes in coronary tone were responsible for changes in ischaemic threshold, it is conceivable that the \(\beta\)-blockers might have 'stabilized' the tone of the coronary arteries. This possible stabilization of the coronary tone may play a role in their effect in preventing major cardiac events. However, the full effect of \(\beta\)-blockers on the circadian distribution of ischaemic threshold and ischaemic episodes could not be assessed in this study as these patients were only partially \(\beta\)-blocked and data on the same patients with and without \(\beta\)-blockers was not available. Previous studies

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**Figure 2** Ischaemic thresholds during daily life (highest and lowest) and during exercise. NS=non significant. (Reproduced with permission from Banai et al.\(^{\text{[19]}}\).)
have shown that in patients effectively treated with \( \beta \)-blockers the number of ischaemic episodes was markedly reduced with disappearance of the morning and afternoon peaks of occurrence\[23\]. The reduction in number of episodes was accompanied by a significant reduction in heart rate, yet some residual ischaemia remained and the authors believe that these ischaemic episodes may have different characteristics.

**Treatment effects**

The effect of nifedipine GITS on the circadian pattern of myocardial ischaemia was assessed by Parmley et al.\[23\] in a group of 207 patients. Nifedipine GITS significantly reduced the weekly anginal attacks and the number of ischaemic episodes and it attenuated the circadian pattern of daily ischaemia. This effect was more striking when nifedipine GITS was combined with a \( \beta \)-blocker which produced a marked attenuation of the morning peak period for ischaemic episodes. In the recently published multicentre Circadian Anti-ischaemia Program in Europe (CAPE) trial, 250 coronary patients received amlodipine once daily or placebo in addition to their background therapy\[24\]. Amlodipine significantly reduced the frequency and duration of daily ischaemia and improved anginal symptoms. The effect of amlodipine was observed throughout the 24 h of the day, thus it reduced the number of episodes but did not alter the circadian distribution of the ischaemic episodes. Stone et al.\[13\] assessed the effect of various anti-anginal drugs on daily and exercise-induced ischaemic episodes. Propranolol suppressed heart rate and significantly reduced the number of ischaemic episodes and, in particular, suppressed the morning increase in the frequency of these episodes. During diltiazem treatment there was a morning increase in heart rate with no apparent increase in the frequency of ischaemic episodes.

The effect of anti-ischaemic medications on the different types of daily ischaemic episodes has been assessed by Andrews et al.\[10\]. Propranolol was more effective in suppressing ischaemic episodes which were associated with an increase in heart rate (types 1 and 2) (65% reduction) than those not associated with heart rate increase (type 3) (45% reduction). In contrast, nifedipine reduced type 1 and 2 episodes by only 27% but caused a marked (58%) reduction of type 3 episodes. Diltiazem therapy resulted in a 35% reduction in types 1 and 2 episodes and a 43% reduction in type 3 episodes. Thus, vasodilators were more effective in preventing ischaemic episodes in which increased coronary tone was believed to play a major role, while \( \beta \)-blockers were more effective in suppressing demand-induced ischaemia.

**Conclusion**

The atherosclerotic coronary artery, which has been regarded for many years as being stable and rigid, has been shown to be capable of dilating and constricting in response to various stimuli\[26-32\]. This vascular response depends on a number of factors, including the integrity of the endothelium, cholesterol level and platelet activity. Dynamic changes in the coronary plaque may result in transient myocardial ischaemia or plaque rupture, leading to progression of coronary disease, unstable angina, myocardial infarction (MI) or even sudden cardiac death. Since all the major events, such as MI and cardiac death, exhibit a circadian pattern which is identical to that of daily ischaemic episodes\[33-35\], it is tempting to speculate that they all share the same mechanism. Reduction of the dynamic changes in coronary vascular tone could transform the active plaques into inactive forms, thus reducing significantly the likelihood of plaque rupture and major cardiac events. View of the assumption that patients with marked variability of their ischaemic threshold have more dynamic changes in their coronary tone, suppression of this activity may lead to improved prognosis for patients with daily occurring ischaemic episodes.

**References**


