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The concept of total ischaemic burden: clinical significance

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Quantification of spontaneous ischaemic episodes during daily activities has been made possible by the introduction of continuous ambulatory ECG (Holter) monitoring. In view of the fact that the large majority of ischaemic patients exhibit both painful and silent myocardial ischaemia, the concept of the total ischaemic burden has been developed. This takes account of the total number, duration and extent of ischaemic episodes over 24 h, in order to provide an assessment of the severity of patients' ischaemic heart disease. Although it is uncertain whether patients with positive exercise tests and both silent and symptomatic ischaemic episodes have a higher risk for myocardial infarction, several studies have shown that these patients have a higher total ischaemic burden. In contrast, despite having high-grade stenosis and positive exercise tests, patients with only silent ischaemic episodes, or without ischaemic episodes during continuous monitoring, seem to experience lower mortality. In general, prognosis is not determined by the presence or absence of anginal pain but by the amount of ischaemia.

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Key Words: Ischaemic heart disease, continuous ambulatory ECG monitoring.

The history of myocardial ischaemia

The phenomenon of ischaemic chest pain was first described in 1772 by Heberden[1] as a type of chest pain that occurred mainly during exercise and vanished 'at the moment (the patients) stand still'. Interestingly, he did not associate the source of this pain directly with the heart. This connection was, however, made several years later by Burns[2]. He explained that anginal pain was due to inadequacy of the blood supply through partial occlusion of the coronary vessels. Due to the fact that during the last century the diagnosis of ischaemic heart disease depended entirely on the presence of anginal symptoms, there was little clinical progress, except for advances in medical treatment. Nitrates were introduced after nitroglycerin was first applied as a homeopathic treatment for headache in 1849[3] under the name of 'glonoine'. Subsequently Field[4] introduced it for the treatment of angina pectoris, due to its anti-spastic effect, Brunton[5] applied amyl nitrate in 1867 and Murrell introduced nitroglycerin as a remedy for angina pectoris in 1879[6]. The success of nitrates in the treatment of angina pectoris is derived from the ability of the endothelium to produce nitrous oxide, an endogenous vasodilating substance[6a,6b].

Subsequently, a major step forward in the diagnosis of ischaemic heart disease was brought about by the introduction of the string galvanometer by Einthoven in 1903[7] and especially by the development of the stepwise exercise test by Master and Offenheimer in 1929[8].

For a long time, specific ECG abnormalities, such as ST-segment alterations, were the only objective signs of ischaemia[9–11] until, in 1958, Möller and Rövick[12] described a haemodynamic equivalent of ischaemia occurring during exercise, i.e. the abnormal increase in pulmonary wedge pressure. Since then it has been confirmed in many studies that an abnormal increase in left ventricular end-diastolic pressure is one of the earliest signs of ischaemia[13,14] and that ischaemia is associated with a decrease in negative and positive dp/dt[15]. These changes usually start very early after the beginning of exercise (within 20 s), depending on the intensity of exercise and the level of ischaemia, and are soon followed by regional wall motion abnormalities[16]. ECG alterations, especially ST-segment depression as a sign of subendocardial ischaemia, tend to occur slightly later (after approximately 2 min) and anginal pain, usually observed after the third min, is the last sign to appear. However, pain is often absent despite an increase in end-diastolic pressure and a positive ECG[13]. Thus, anginal pain has to be regarded as a late-onset sign of ischaemia (Fig. 1).

Similar haemodynamic changes have been described by Chierchia *et al.* in patients with unstable angina[17]. In these patients, left ventricular end-diastolic pressure was abnormally increased (to 16·5 mmHg), especially during symptomatic ischaemic episodes

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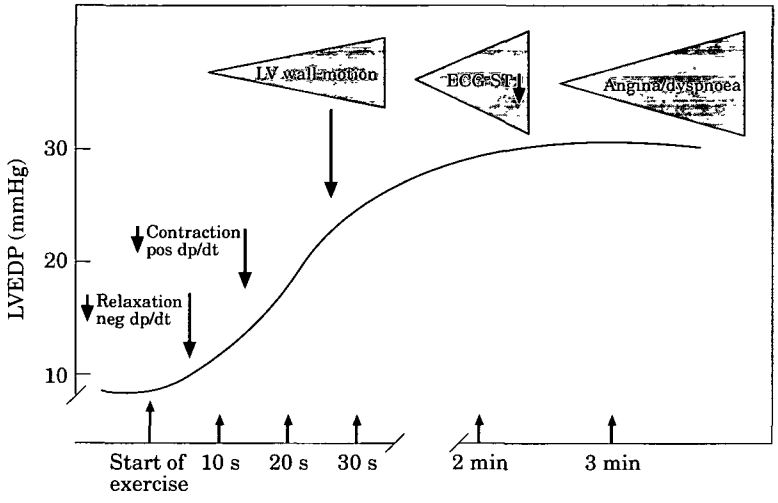

Figure 1 **Sequence of abnormal haemodynamic and mechanical events during exercise-induced ischaemia. Ordinate: change in left ventricular end-diastolic pressure (LVEDP), indicated by the thick line. Abscissa: time course in s and min. The sequence as well as the changes are derived from data obtained during heart catheterization[13,15].**

(typical angina pectoris and ST depression), while during asymptomatic episodes haemodynamic parameters remained normal (left ventricular end-diastolic pressure during ischaemia 5·9 mmHg). The same was true for changes in peak positive dp/dt (−395 vs −252 mmHg . s^{-1}, respectively) and peak negative dp/dt (−413 vs −259 mmHg . s^{-1}, respectively) ($P<0·001$). This difference in left ventricular haemodynamic parameters between symptomatic and asymptomatic patients was in contrast to that observed in patients with stable angina, in whom no such symptom-dependent haemodynamic differences were found during exercise. However, during 24-h continuous ambulatory ECG monitoring in stable angina patients, asymptomatic ischaemic events were found to be of longer duration than symptomatic episodes (14·2 vs 9·3 min, respectively) ($P<0·001$)[18]. Similarly, ejection fraction during exercise was decreased in symptomatic stable angina patients and increased in those who were asymptomatic[19].

Quantification of spontaneous ischaemic episodes during daily activities only became possible after the introduction of continuous ECG recording over 24 h by Holter in 1961[20]. At first this technique was applied primarily to the study of life-threatening, mainly ventricular arrhythmias[21], as there were still considerable technical difficulties with the continuous recording of ST-segment changes[21,22]. These difficulties included the selection of optimal ECG leads, together with their stabilization and beat-to-beat analysis. As a consequence, ST-segment recording really started in the 1970s[23,24], initially using manual analysis of ECGs, and it became popular in the 1980s when assisted by fully automated ST-segment analysis[25–27]. The phenomenon of silent ischaemia was described for the first time by Stern and Tzivoni[24] who utilized a manual analysis, followed by a number of other investigators[18,22,23,26,28]. Some of these studies also included a comparison of the extent of coronary artery disease (CAD), as assessed by coronary angiography, with the occurrence of silent and clinically manifest ischaemic episodes. They confirmed the correlation between the incidence of silent episodes and the anatomic extent of CAD (Fig. 2)[29], i.e. the greater the extent of CAD, the higher the number of symptomatic episodes observed[30]. Accordingly, subsequent studies performed with continuous ambulatory ECG monitoring reported that, in angina patients, only approximately 25–30% of daily ischaemic events are accompanied by typical chest pain. The remaining episodes are expressed solely through ST-segment changes, especially ST depression (≥0·1 mV over at least 1 min)[27,31,32] and would be missed without continuous ECG monitoring. In addition, in approximately 3–5% of patients with CAD, ischaemic events are completely silent and patients are, therefore, completely unaware of their disease[33–35]. In most patients, however, ambulatory ECG monitoring shows the occurrence of both silent and manifest episodes, although the former occur with a higher frequency. In a small group of patients symptomatic episodes without ECG signs of ischaemia can even be observed during ambulatory ECG monitoring, which should probably also be included as true ischaemic episodes[32,36].

Causes and mechanisms leading to silent myocardial ischaemia

At present, three main causes are thought to be responsible for the absence of anginal pain during silent ischaemic episodes.

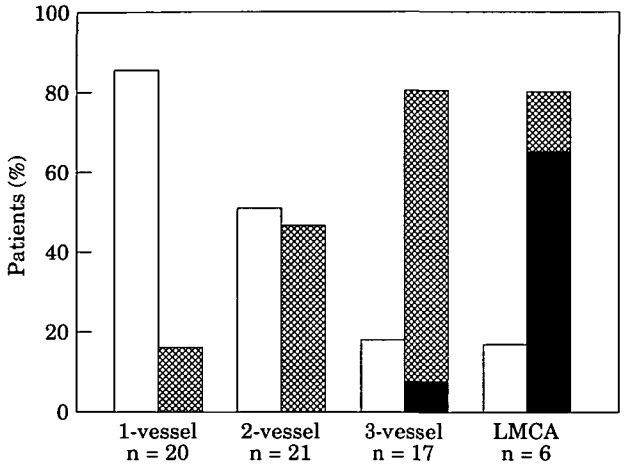

Figure 2 **Percentage of patients with only asymptomatic episodes (□), with mixed, i.e. asymptomatic and symptomatic (▨) or only symptomatic episodes (■) and typical ST-segment depression during Holter monitoring. Patients are classified according to the anatomical changes of coronary arteries as found during angiography into single-, double- and triple-vessel disease and isolated left main stem stenosis (LMCA). Predominant asymptomatic events were seen mainly in single-vessel disease, whereas in triple-vessel disease predominantly mixed types or in severe left main coronary artery disease mainly symptomatic episodes were observed. (Reproduced with permission from Lichtlen and Hausmann[29].)**

Anatomical causes

In order to provoke anginal pain, a minimum amount of pain-producing substances, which are not yet clearly identified but may include hydrogen ions, kinins, histamine, creatinine, prostaglandins, serotonin, adenosine, potassium and substance P, must be present. The liberated amount depends, above all, on the size of the ischaemic area in the myocardium; the larger the area, the higher the incidence of events. To a certain degree, however, the duration of ischaemic events is determined by the presence or absence of anginal pain which can restrict physical activity[18,29,30]. The highest incidence of symptomatic episodes (approximately 70%) is found in patients with left main coronary artery stenosis, the highest incidence of asymptomatic episodes is in patients with single-vessel disease, mainly of the left anterior descending (LAD) branch (Fig. 2)[29].

Functional causes

The level of coronary blood flow in the ischaemic area influences pain by determining the speed by which pain-producing substances are washed out of the ischaemic area. Depending on the degree of stenosis, on the extent of CAD and the duration and location of ischaemia, high- and low-flow ischaemia can be distinguished[37].

Neurogenic causes

Several studies[38–40] have revealed that neurogenic factors play a considerable role in silent ischaemia. The inhibitory pain-modifying system possibly involves endogenous opiates (endorphins). Weidinger *et al.*[41] and Droste and Roskamm[38,39] have found significant differences in plasma β-endorphin levels between patients with symptomatic and asymptomatic ischaemic episodes. In addition, in Droste's study of 20 patients with exclusively asymptomatic ischaemic episodes, only four experienced pain with an electrical stimulus of 0·5 mA or less, in comparison with 10 of 22 patients with symptomatic episodes. The mean electrical pain thresholds in this study were 0·57 mA and 1·04 mA in symptomatic and asymptomatic patients, respectively[39]. Nevertheless, the relation between endorphins and pain behaviour still remains unclear and requires further elucidation, at least with regard to silent ischaemia.

Characteristics of ischaemia during exercise testing and ischaemia in daily life

In the majority of studies, significantly more patients exhibit ischaemic ECG signs during exercise testing than during 24-h continuous ambulatory ECG monitoring, when undergoing both tests successively[42–47]. Continuous ambulatory ECG monitoring has a sensitivity of approximately 70% vs 86% for exercise tests. Nevertheless, in a small group of patients, ischaemic events seem only to be detectable during continuous monitoring[44].

Interestingly, in our experience, patients with completely asymptomatic but positive exercise tests also had significantly fewer symptomatic episodes during 24-h continuous ambulatory ECG monitoring (10·9%) than those with symptomatic positive exercise tests (32·1%) ($P<0·001$)[43]. Furthermore, 69% of patients with asymptomatic exercise tests had exclusively asymptomatic ischaemic episodes during continuous ambulatory ECG monitoring in contrast to only 34% of patients with symptomatic tests.

In addition, as shown in most of the studies comparing spontaneous ischaemic episodes with those induced by exercise, the average heart rate at onset of ischaemia (appearance of ST-segment depression >0·1 mV) was significantly lower during continuous ambulatory ECG monitoring (average 98 beats . min^{-1}) than during exercise testing (average 110 beats . min^{-1})[26,43,48,49]. Accordingly, patients who only exhibited typical ST depression during exercise testing above a heart rate of 120 beats . min^{-1} were significantly less likely to have a positive continuous ambulatory ECG monitoring test (55·6%) than those with typical ECG signs at heart rates <120 beats . min^{-1} (86·8%) ($P<0·001$)[49]. A clear correlation between the number of ischaemic episodes on

ambulatory ECG monitoring and time to onset of ischaemia in exercise tests has been found. For example, 44 patients in whom the exercise test became positive before the 5th min had more spontaneous ischaemic episodes during continuous ambulatory ECG monitoring ($3{\cdot}6\ day^{-1}$) than those who became positive after 5 min ($2{\cdot}4\ day^{-1}$, $P<0{\cdot}05$)[50]. Hence, due to its higher sensitivity (86·2% positive during exercise, 69·7% during continuous monitoring), exercise testing is more useful for diagnosing the presence of CAD. Furthermore, it is also a predictor for the incidence of spontaneous ischaemic events and together with continuous ambulatory ECG monitoring, its value for predicting future coronary events is considerable. Accordingly, in a series of 166 patients with angiographically proven CAD (stenosis >70% in at least one coronary artery) and a positive exercise test and 102 with positive continuous ambulatory ECG monitoring[50], the most powerful determinants for the prediction of ischaemia in daily life were defined as follows: (1) during exercise tests a low heart rate at onset of ST-segment depression (112 vs 121 beats . min^{-1}) ($P<0{\cdot}001$) and a short duration until the onset of ischaemia (4·8 vs 5·7 min) ($P<0{\cdot}05$) as well as shorter exercise time (7 vs 7·7 min) ($P<0{\cdot}05$); (2) high R-wave amplitudes in leads CM3 and CM5 during continuous ambulatory ECG monitoring (17·2 vs 13·8 mm) ($P<0{\cdot}0001$); (3) a high-grade stenosis in the LAD branch (76 vs 59%) ($P<0{\cdot}05$). There was, however, no difference in the maximum ST depression (2·4 vs 2·2 mm) or in resting left ventricular ejection fraction (65% vs 64%).

The circadian rhythm of ischaemic events

One of the most important findings to be derived from 24-h continuous ambulatory ECG monitoring is the circadian distribution of spontaneous ischaemic episodes[18,23,26,51–54] (Fig. 3). There is a peak in the incidence of ischaemic episodes between 0800 and 1000 h and a second, smaller peak between 1600 and 1700 h. The incidence of ischaemic events is lowest during the night, especially between midnight and 0600 h. The circadian rhythm of ischaemia has been closely correlated with that of heart rate[25,48,52] and with the incidence of myocardial infarction (MI)[55,56], sudden coronary death[56,57] and, to a lesser extent, with ventricular arrhythmias[58,59]. All these events occur with a high frequency in the early morning hours, when the incidence of ischaemic events is at its maximum. Interestingly, similar distributions, peaking in the early morning, have also been observed for arterial blood pressure[60], catecholamines[61], cortisol plasma levels[62], platelet aggregability[63,64] and fibrinolytic activity[65]. Therefore, the morning hours appear to be associated with the highest risk for ischaemic complications in patients with severe CAD.

The clinical relevance of the total ischaemic burden

The concept of the total ischaemic burden, defined by Cohn in 1986[66], encompasses all episodes of ischaemia, both silent and symptomatic. It includes both ischaemia due to reduced oxygen supply (primary ischaemia) and due to increased oxygen demand (secondary ischaemia) or a combination of the two (mixed ischaemia)[66] and has led to a re-evaluation of therapeutic goals for patients with CAD. Hence, the term total ischaemic burden includes the total number of spontaneous ischaemic episodes (ST-segment depression $\geq 0{\cdot}1$ mV, duration ≥ 1 min, separated from the next episode by ≥ 1 min) and their total duration over 24 h. It includes both the nocturnal phase, with a generally low heart rate and relatively few ischaemic events, mostly of the primary type (reduced oxygen supply) and the daytime phase, with an approximately five-fold higher incidence of ischaemic events[50] (mostly due to increased demand) and a mild increase in heart rate provoked by different types of physical exercise. This concept recognizes all types and electrocardiographic equivalents of ischaemia, including ST depression as an expression of subendocardial ischaemia during exercise and at rest and ST elevation as an expression of transmural ischaemia during coronary occlusion, for example during coronary artery spasm. Only the few episodes which are associated with symptoms alone (see above)[32] are not included in the total ischaemic burden. Obviously, the concept of total ischaemic burden has both a prognostic[67,68], as well as a therapeutic value[69,70].

The prognosis of coronary artery disease — its dependence on the type of ischaemia and on total ischaemic burden

In patients with stable angina undergoing both exercise tests and 24-h continuous ambulatory ECG monitoring, it has been shown that prognosis is worse when both tests are positive, especially when they are accompanied by pain and when the number of episodes, especially of silent ones, is increasing ($P<0{\cdot}05$–$0{\cdot}01$)[31,71,72].

Early prognostic information came from a study by Cohn *et al.* in 1981[68] which involved 44 patients with angiographically proven CAD (one or more stenoses >75%), 32 with a prior MI, who were asymptomatic at the time of cardiac catheterization, matched with 127 symptomatic patients with similar coronary anatomy and ventricular function. Thirty-one of the 44 asymptomatic patients had exercise tests and 17 of them (38·6%) were positive but without angina. Of the 127 symptomatic patients, 96 underwent exercise tests and 48 (50%) were positive. Over a 7-year follow-up period (mean 3·5 years) survival in the asymptomatic group (81%, mortality 2·7% . $year^{-1}$) was significantly higher than in

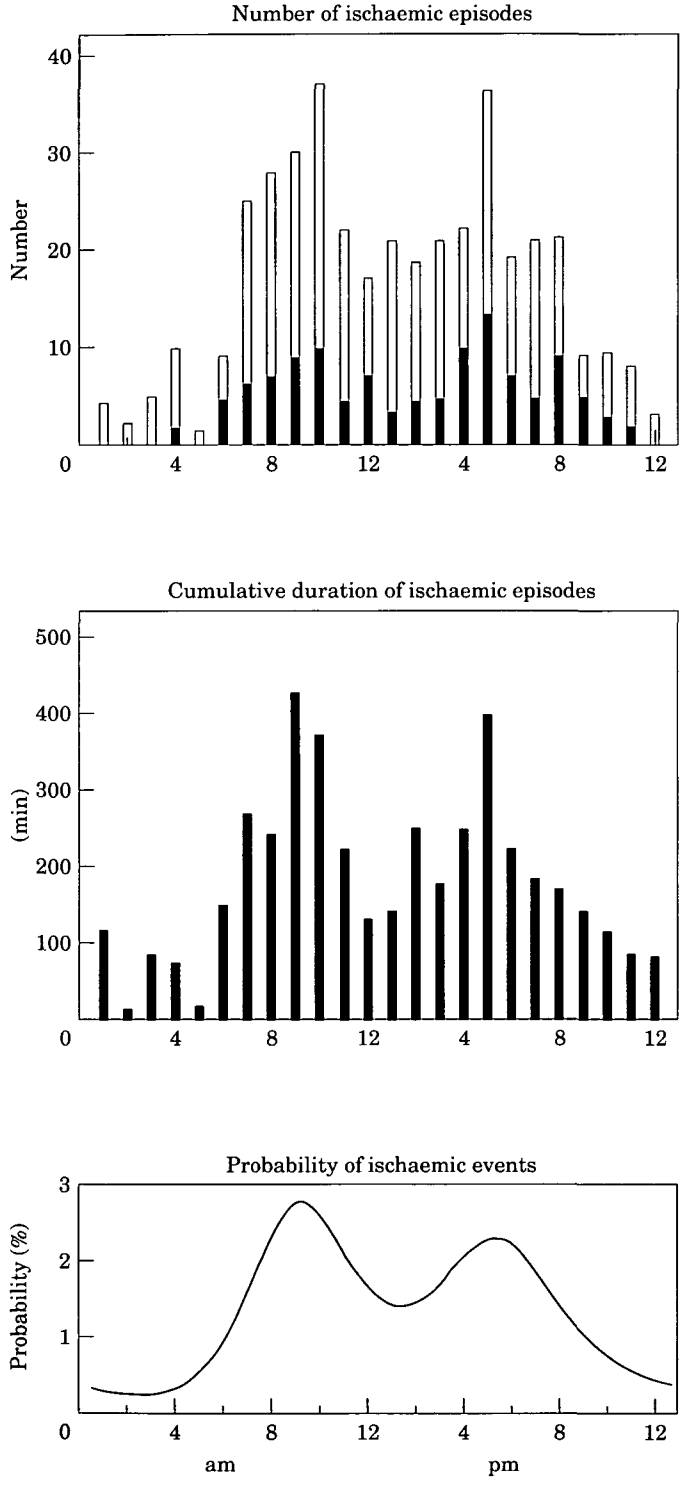

Figure 3 **Circadian variation of ischaemic episodes in patients with stable coronary artery disease. Top: number of ischaemic episodes; middle: cumulative duration of ischaemic episodes; bottom: probability of the occurrence of ischaemic episodes during time intervals of 5 min (goodness of fit=0·326). □= silent; ■=symptomatic. (Reproduced with permission from Hausmann *et al.*[52].)**

Table 1 Coronary events in patients with stable coronary artery disease during follow-up of 12·5 ± 7·5 months. (Reproduced with permission from Rocco* et al.*[71])

	STD	No STD
Death	2	0
Myocardial infarction	4	0
Unstable angina	3	1
Revascularization for progressive symptoms	11	0
Total	20	1

STD=ST-segment depression on monitoring.

the symptomatic group (62%; mortality 5·4%/year^{-1}; $P<0·05$). Thus, independent of the exercise test, the additional presence of symptomatic episodes rendered the prognosis worse in patients with stable CAD, indicating that the presence of angina pectoris may be an independent determinant of prognosis.

Additionally, in a study by Rocco *et al.*[71] in 86 patients with stable CAD and positive exercise tests, only 49 (57%) also had positive continuous ambulatory ECG monitoring (426 ischaemic episodes, 8·6 . patient^{-1}, 60 (14%) episodes with pain). All patients were followed over a maximum of 25 months (mean 12·5 ± 7·5 months). In this study, the presence of ischaemia in ambulatory monitoring, independent of the presence of symptoms, was a significant predictor for an unfavourable outcome, whereas exercise testing alone was not (Table 1).

Similarly, a study by Tzivoni *et al.*[45], including 224 patients who, after acute MI, underwent both exercise tests and continuous ambulatory ECG monitoring and who were followed from 12–58 months (average 28 months), showed that the lowest event rate (8·5%) (cardiac death, recurrent MI, unstable angina, revascularization) was observed in patients who were negative for both tests. Patients with negative Holter monitoring, but a positive exercise test, had a 20% event rate, whereas patients with both tests positive had an event rate of 51% ($P<0·0001$). Furthermore, patients with ischaemia in daily life, when compared with those with a positive exercise test only, had a significantly higher incidence of all cardiac events (30% vs 11%, $P<0·0005$), unstable angina (13·5% vs 3·3%, $P<0·005$), interventions such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) (22% vs 1·3%; $P<0·0001$) and of cardiac death (5·4% vs 2·6%). However, the difference in recurrent MI (10·8% vs 4·7%) was not significant. Therefore, in patients with stable angina, applying continuous ambulatory ECG monitoring increases the prognostic value of exercise testing especially after MI.

Interestingly, in contrast to stable angina, most of the prognostic studies in patients with unstable angina indicate a worse prognosis when only silent episodes are present during Holter monitoring, especially when the frequency of these events is high[72].

In a classic study, Gottlieb *et al.*[28] analysed the probability of not experiencing an unfavourable outcome (MI or revascularization for symptoms) in patients with unstable angina who underwent 48-h continuous ECG monitoring while in the coronary care unit. Thirty-seven patients had only asymptomatic ischaemia, while 33 had symptomatic episodes. In the follow-up over 30 days, patients with only silent ischaemia had a significantly higher number of clinical events (16 vs 4; $P<0·01$), including new MIs (6 vs 1; $P<0·005$) and urgent revascularization procedures (10 vs 3; $P<0·02$). When they correlated total ischaemic duration over 48 h to the clinical outcome, they found that patients with a total ischaemic time of $\geq$60 min . 24 h^{-1} had a worse prognosis than patients with <60 min ($P<0·04$). Thus, in this study in patients with unstable angina, 'silent ischaemia was found to be the variable most predictive of unfavourable outcomes'.

These authors also followed the same patients over 2 years[31] (Table 2) and found that the best prognosis (i.e. the highest probability of remaining free of events over 2 years) was found in patients both without silent or symptomatic ischaemia. Conversely, the worst outcome was seen when both types of ischaemia (silent and symptomatic) were present. Hence, in these unstable patients, the presence of silent ischaemia predicted the worst outcome over 2 years, despite the use of medical therapy.

Table 2 Two-year adverse clinical outcome for unstable angina patients with and without silent ST-segment changes on initial 48-h Holter monitoring. (Reproduced with permission from Gottlieb* et al.*[31])

Adverse clinical outcome	Group I Silent ischaemia (n=37) (%)	Group II No silent ischaemia (n=33) (%)	*P* value*
Cardiac death	2	0	<0·01
Non-fatal MI	8 (27)	1 (3)	
CABG or PTCA for symptoms	11 (30)	5 (15)	<0·05
Total	21 (57)	6 (18)	<0·001

*Derived from Kaplan–Meier analysis. Breslow test.
CABG=coronary artery bypass grafting; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty.

Similarly, Nademanee *et al.*[73] found that a favourable clinical outcome was observed in only 6% of patients with a total ischaemic burden >60 min . 24 h^{-1} in contrast to 70% of those with a total ischaemic burden <60 min . 24 h^{-1} and 95% of those without silent ischaemia ($P<0.001$). In addition, these authors concluded that in unstable angina, 'silent ischaemia persisting after or (present) in spite of medical therapy is associated with an adverse short-term prognosis'. Therefore, in contrast to stable angina, patients with unstable angina and mainly silent ischaemia during continuous ambulatory ECG monitoring have a higher risk for coronary events than those with negative continuous monitoring or symptomatic episodes.

The prognosis based on exercise testing results alone seems to differ considerably between studies. In the extensive survey of the Coronary Artery Surgery Study (CASS) registry[74], which included 2982 patients who all underwent coronary arteriography, exercise testing proved to be unreliable in the assessment of prognosis. There were 424 patients, in whom exercise testing led to typical ST depressions but without angina pectoris (group I), 232 patients in whom angina pectoris occurred without typical ECG signs (group II), 456 patients with angina pectoris and typical ST depression (group III) and 471 patients with a negative exercise test, i.e no ST depressions and no angina pectoris (group IV). Interestingly, the 7-year survival rate did not differ between groups I, II and III (76%, 77% and 78%, respectively). However, it was significantly higher in group IV (88%; $P<0.001$). Therefore, in this study, outcome was not dependent on the presence of both ST depressions and angina during exercise, but only on one of these ischaemic manifestations, indicating that the presence of angina alone was of equal prognostic value as ST-segment changes alone. This was in accordance with the observations of Krantz *et al.*[36] and Hausmann *et al.*[51] during 24-h continuous ambulatory ECG monitoring. In addition, in CASS, in group I patients with only silent ischaemia, survival was clearly dependent on the severity of CAD ($P<0.001$); for triple-vessel disease it amounted to 50% only vs 70% for double- and 90% for single-vessel disease.

A critique of the total ischaemic burden

In order to evaluate the importance of total ischaemic burden, Mulcahy *et al.*[75] prospectively followed 172 coronary patients for 39 months (average 24·5 months). The diagnosis of CAD was based not on angiography, but instead on clinical manifestations of coronary disease and all patients underwent exercise tests and 48-h continuous ambulatory ECG monitoring. Seventy-five patients (44%) had previous MIs, 23 (13%) had undergone CABG or PTCA and 161 (94%) were on antianginal treatment. One-hundred and four patients (61%) had a positive exercise test, 72 (42%) experienced ischaemic events during continuous ambulatory ECG monitoring, 63 (36%) were positive in both tests and 59 (33%) were negative in both tests. During follow-up there were 27 events (16%), including five deaths (3%) (three cardiac) and six non-fatal MIs (3%); six patients developed unstable angina (3%) and 10 needed revascularization (6%). Of the nine patients reaching objective endpoints (three deaths, six MIs), only two had evidence of ischaemic events on continuous ambulatory ECG monitoring. From this, the authors concluded that, in this group of patients, there was no advantage associated with the use of continuous ambulatory ECG monitoring for prognostic reasons. This study was probably inconclusive due to the short follow-up as well as the lack of objective signs of CAD other than those observed with ECG. The authors assumed that the lack of association between transient myocardial ischaemic events and non-fatal MI was due to the fact that plaque rupture and the ensuing acute MI often occurs in small, non-ischaemic plaques (stenosis <50%), an observation confirmed in a prospective angiographic study with repeated coronary angiograms over 3 years[76]. However, Mulcahy and coworkers agreed that patients with ischaemia on exercise were more likely to develop symptoms requiring intervention.

In summary, most of the studies discussed have confirmed the prognostic importance of silent ischaemia when observed during continuous ambulatory ECG monitoring, especially in patients with unstable angina. There are, however, differences between studies based on exercise tests alone; some have shown a worse prognosis when chest pain is present in addition to ST-segment depression[77] while others, like the CASS study, found that pain did not have additional prognostic value[74]. In general, however, most of the studies demonstrated that the addition of 24–48-h periods of continuous ambulatory ECG monitoring has significant additional prognostic value in patients with stable angina, especially if ischaemic episodes are accompanied by pain, in contrast to those with unstable angina in whom prognosis is worsened by silent episodes.

The importance of total ischaemic burden for control of treatment

Until the introduction of continuous ambulatory ECG monitoring, direct control of anti-ischaemic drug treatment over a long period of time had to rely on the incidence of episodes of angina pectoris and/or on the measurement of nitroglycerin tablet consumption. Objective quantitative assessments of ischaemic events have now been made possible by assessing the total ischaemic burden before and during treatment. This has had several consequences. Above all, the issues of the long-term effect of ischaemic events, protection against structural alterations and improvement of symptoms through drug treatment must be revisited[69]. In recent years, several histological studies have suggested that

structural impairment is brought about by repeated ischaemic events of longer duration[78–81]. For example, Krayenbühl *et al.*[79] analysed histological probes harvested from subendo- and subepicardial regions during CABG in patients who demonstrated both hypokinetic and normokinetic areas during exercise. They found significantly more interstitial fibrosis in hypokinetic than in normokinetic subendocardial areas (28·6% vs 18·2%), whereas no differences were observed between the epicardial normo- and hypokinetic zones (18·6% vs 16·2%). There were also no differences in muscle fibre diameters (28·1 μ in normokinetic vs 29·2 μ in hypokinetic subendocardial areas). They concluded that repeated ischaemic events can lead to an increase in fibrosis in the subendocardial ischaemic area and probably to irreversible focal damage.

Analysis of histological probes taken from ischaemic areas during CABG in patients with severe CAD also showed severe interstitial fibrosis as well as marked intracellular changes[80,81]. These concern both sarcomeres (distortion of contraction bands and lack of contractile material in 75% of cases) and mitochondria (irregular shape in 37% of cases), as well as atrophic cell degenerations (vacuoles with debris, myelin bodies), and microvessel changes, such as swollen endothelial cells and thickened basement membranes.

These findings of ischaemia-induced structural changes led to the assumption that intensive anti-ischaemic treatment, with the aim of reducing the total ischaemic burden to a minimum, might protect against structural myocardial damage and in turn prevent clinical events such as non-fatal MI. Hence, several studies are underway to analyse the influence of anti-ischaemic drug treatment on outcomes of CAD, such as sudden coronary death and fatal and non-fatal MIs[82–84]. One of the principal aims of these studies is to prevent the morning increase of silent ischaemic events and thus reduce non-fatal MIs, with a view to improving prognosis and outcome[32,47]. It is promising that a significant reduction in symptomatic and asymptomatic ischaemic events has been demonstrated with a wide variety of anti-ischaemic drugs, such as long-acting oral nitrates, β-blockers and calcium antagonists[69]. In this context, however, long-acting drugs, such as amlodipine, which has a plasma half-life of 30–50 h, are of particular importance[70]. Profound anti-ischaemic effects can only be achieved with constant blood levels over 24 h with drugs that do not produce tolerance, such as calcium antagonists and/or β-blockers.

In general, from the many medical intervention studies that have employed continuous ambulatory ECG monitoring over the last 15 years, one can conclude that, in stable angina, monotherapy leads to an average reduction of ischaemic events of approximately 43% for calcium antagonists, 63% for β-blockers and 52% for nitrates[70]. Combinations of nitrates with β-blockers or calcium antagonists show a further slight reduction to approximately 66%[70]. Combination therapy seems to be better than monotherapy, as shown most recently in the Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS)[85] as well as in the Circadian Anti-ischemia Program in Europe (CAPE) study[86]. In unstable angina, calcium antagonists achieve a reduction of events up to 75% in comparison with only about 50% with β-blockers[70]. Obviously, complete freedom from ischaemic events is only rarely achieved by medical therapy and the question arises as to whether a 50–60% reduction is sufficient to also suppress structural deterioration induced by ischaemia. In the near future these important questions have to be resolved by definitive studies with long-acting drugs, alone or in combination, analysing their influence on clinical improvement, as well as changes in cardiovascular structures.

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