Myocardial infarction, circadian rhythm and delay in hospital admission

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Summary
Circadian variations have been observed in the onset of acute coronary syndromes including acute myocardial infarction. We studied 422 acute myocardial infarction patients who presented to the coronary care unit of General Hospital Kuala Lumpur. Of the 318 (75.4%) patients whose data was complete, a circadian rhythm with bimodal peak was demonstrated. The second quarter of the day i.e. 6.00 a.m. to 12 noon was shown to have a significantly increased frequency of onset of acute myocardial infarction (p <0.05).

Time delay in presenting to the hospital was also determined. This showed that 56.8% of acute myocardial infarction patients presented early, within four hours of the onset of symptoms. By six hours, more than 71% had sought hospital care. This early presentation to the hospital may offer a realistic opportunity for optimal thrombolytic therapy should this treatment modality be offered as routine to infarct patients.

Key words: Acute myocardial infarction, circadian rhythm, delay in hospitalisation.

Introduction
Human circadian rhythms have been alluded to, since the time of Hippocrates. Body temperature, circulating hormonal levels, exacerbations of hay fever and bronchial asthma are among the more well-known biologic phenomena which vary with time over a 24-hour period.

Many such temporal variations may have potential effects on the cardiovascular system, particularly when even seemingly minor changes can have important and crucial effects on an already ischaemic myocardium with critical stenoses of its coronary arteries. We know that plasma cortisol peaks at awakening time, plasma catecholamines reach maximal levels during the later morning hours together with their attendant increases in heart rate and blood pressure. Furthermore, at awakening time, abrupt rises in blood pressure have been documented. Lately, increase in platelet aggregability and a decrease in fibrinolytic activity have been demonstrated in the early morning hours. In fact, morning increase in cardiac output and myocardial contractility has been shown by systolic time intervals. All these factors may influence the cardiovascular response at varying times during the day, and be causally related to clinical outcomes i.e. myocardial infarction, sudden cardiac death, and myocardial ischaemia.
Rocco et al\textsuperscript{16} have recently reviewed rather convincingly, the evidence for circadian rhythms and their effects on coronary artery disease. We prospectively studied myocardial infarction patients admitted to the coronary care unit to determine if such a circadian pattern did indeed occur with our Malaysian population.

We further looked at the time delay from the onset of myocardial infarction, before patients present themselves to the hospital for treatment. We felt that this was important because of the benefits being increasingly shown with the early use of thrombolytic agents for the purpose of myocardial salvage and long-term prognosis in heart attack patients.\textsuperscript{17,18,19,20}

**Methods and materials**

We studied all patients who were admitted to the coronary care unit of the General Hospital Kuala Lumpur during a 8-month period, from May to December 1987.

**Onset of myocardial infarction:** By means of a standard questionnaire and individual review of each patient's history at presentation, the onset of severe ischaemic type chest pain was documented where possible from the patient himself or from close relatives where the patient was unable to, according to the circumstances of admission. Patients who presented with severe dyspnoea as a symptom of acute pulmonary oedema later proven to be caused by a fresh myocardial infarction were also included — the onset of the acute breathlessness was taken as the time of onset of the myocardial infarction. [Table I shows the distribution of the presenting symptoms.]

**Table I**

<table>
<thead>
<tr>
<th>Presenting feature</th>
<th>Number of infarct patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central chest pain</td>
<td>217 (68.2%)</td>
</tr>
<tr>
<td>Acute dyspnoea with chest tightness</td>
<td>28 (8.8%)</td>
</tr>
<tr>
<td>Acute pulmonary oedema</td>
<td>42 (13.2%)</td>
</tr>
<tr>
<td>Cardiovascular collapse</td>
<td>31 (9.8%)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>318 (100%)</strong></td>
</tr>
<tr>
<td>Data unavailable</td>
<td>104</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>422</strong></td>
</tr>
</tbody>
</table>

**Time at presentation to hospital:** The time of presentation to the hospital casualty of all patients were documented and confirmed with the admission forms.

**Time delay from onset of myocardial infarction:** This was computed from the difference between the time of onset of symptoms and the time of presentation to the hospital. This time difference was considered the time delay from the onset of actual acute cardiac infarction, and approximated to the nearest half-hour for statistical considerations.
Criteria for inclusion as acute myocardial infarction: Myocardial infarction was diagnosed when two or more of the following criteria were documented:

1. Typical central ischaemic chest pain lasting more than 30 minutes;
2. Typical serial electrocardiographic changes of the ST–T segment, with or without Q waves, in more than two leads;
3. Serial elevation of cardiac enzymes to at least twice the upper limit of normal in two or all three enzymes: creatine kinase, lactic dehydrogenase and aspartate transaminase.

Patients admitted for all other coronary syndromes of unstable angina or other diagnoses as listed elsewhere were excluded from the analysis.

Statistical analysis
The frequency of the time of onset of myocardial infarctions was plotted against time over a 24-hour period. Each hourly block was then compared by chi-square analysis with the expected mean hourly frequency. The frequency of time of presentation to the hospital was also plotted. Finally, the time delay from onset of myocardial infarction to time of presentation to the hospital was analysed. A P value of <0.05 was considered significant.

Results

Ethnic and age characteristics
Of the 1141 patients admitted to the coronary care unit during this period, 422 had acute myocardial infarction based on the criteria above. Of these 422, 335 (79.4%) were males and 87 (20.6%) were females, whose ages ranged from 24 to 85 years, with a mean age of 55.4 years. The ethnic distribution were as follows: Malays 138 (32.7%), Indians 162 (38.4%), Chinese 102 (24.2%), and others 20 (4.7%).

However, a large group of 104 patients (24.6%) could not offer a definite time of onset of either chest pain or dyspnoea or collapse. 40 of these however, had records of their time of presentation to hospital. Some 36 patients could not be sure of the time of onset of symptoms as they presented some 24 hours or more afterwards.

Among those 104 who could not give a good history, many presented to casualty in collapsed states, 42 (40.4%) died subsequently, the majority from massive infarcts with cardiogenic shock or terminal arrhythmias. Among those 318 who were able to give the time of onset of their symptoms, 20 (6.3%) subsequently died.

Analysable data were thus obtained from 318 patients regarding their time of onset of myocardial infarction, 358 patients regarding their time of presentation to Casualty, and 351 patients regarding their delay (318 plus 34 who gave estimates of their symptom onset in days) in coming to hospital.

Hourly variation in the onset of myocardial infarction: As can be seen from Figure 1, two hourly peaks could be discerned from the distribution, one at 7.00 a.m. and the other at 8.00 p.m. The increased frequency at these times of onset of myocardial infarction was statistically significant (p <0.025 and p <0.05, respectively) when compared to the expected average frequency of 13.25 per hour.
Fig. 1: Hourly variation in the onset of acute myocardial infarction among patients presenting to General Hospital Kuala Lumpur

(* = P < 0.025, ** = P < 0.05)

Furthermore, if the day was divided into 6-hourly blocks (Table II), the second quarter (from 6.00 a.m. to 12 noon) showed a statistically significant increased frequency above the expected mean of 79.5 (p < 0.05).

Because of the smaller numbers involved, when the data were analysed with regards sexual distribution, no significant trend was noted among the female sample alone (p > 0.05). Although among the men, there was some trend suggesting a morning peak, no significant hourly increase was noted, when the male sample (241 of the 318) was taken alone. The six-hourly blocks however showed a non-significant increased frequency during the second quarter of the day (p = 0.08, see Table II).

Table II

Six-hourly distribution of onset of myocardial infarction

<table>
<thead>
<tr>
<th>Time</th>
<th>Total Frequency (%)</th>
<th>Male Frequency (%)</th>
<th>Female Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 MN – 6.00 a.m.</td>
<td>71 (22.3) NS</td>
<td>54 (22.4) NS</td>
<td>17 (22.1) NS</td>
</tr>
<tr>
<td>6.00 a.m. – 12 noon</td>
<td>97 (30.5) *</td>
<td>74 (30.7) **</td>
<td>23 (29.9) NS</td>
</tr>
<tr>
<td>12 noon – 6.00 p.m.</td>
<td>78 (24.5) NS</td>
<td>58 (24.1) NS</td>
<td>20 (26.0) NS</td>
</tr>
<tr>
<td>6.00 p.m. – 12 MN</td>
<td>72 (22.6) NS</td>
<td>55 (22.8) NS</td>
<td>17 (22.1) NS</td>
</tr>
<tr>
<td>TOTAL 24 hours</td>
<td>318 (99.9)</td>
<td>241 (100)</td>
<td>77 (100.1)</td>
</tr>
</tbody>
</table>

(NS: not significant; *: P < 0.05; **: P = 0.08)
Ethnic and age variations: From the above computations, this eight month sample when further characterised by ethnic and age distributions yielded too small numbers for useful analysis by statistical methods. No trend was seen however to suggest any significant difference between the various races or age groups in this population sample.

Time at presentation to hospital: As can be seen in Figure 2, most arrivals at the hospital casualty took place after 10.00 a.m. through to the early afternoon to 4.00 p.m. Most of these popular hours showed statistically significant increased frequency. There was a definite trend of avoiding presentation to the hospital during the early hours of the morning especially from 4.00 a.m. to 8.00 a.m. This may in part be due to the reluctance to seek medical assistance during these unearthly hours as well as perhaps to avoid the morning rush hours and traffic jam.

Time delay from onset of myocardial infarction to hospital arrival: As is evident from Figure 3, most of our patients presented fairly early to the hospital after the onset of myocardial infarction. This may signify the seriousness and alarm with which most heart attack patients attribute to their symptoms. In fact, 56.8% of all heart attack patients presented to the hospital within four hours, and 71.6% within six hours of symptoms. By seven hours, three-quarters had sought treatment at the hospital. Contrary to popular belief, most heart attack patients appeared to understand the significance of their symptoms by presenting early, although one may ask if they were early enough.

Discussion
Our preliminary survey of just 422 patients showed some interesting results which concurred well with previous reports. It would appear that even in our Malaysian population, the occurrence of myocardial infarction followed a circadian rhythm with a bimodal distribution, with two

![Graph showing time of arrival at hospital](image)
Fig. 3: Time delay from the onset of acute myocardial infarction to the time of presentation to General Hospital Kuala Lumpur.

A. Cumulative frequency of delay time;
B. Frequency in delay time by hours.

peak periods about 12 hours apart i.e. about 7 a.m. and 8 p.m. This finding agrees very well with those of others. In an earlier population survey, Master found a peak incidence of acute myocardial infarction at 10 a.m. In another study of 1200 patients, the onset of acute myocardial infarction (based also on the commencement of symptoms), a bimodal distribution with a major peak around 9 a.m. and a secondary peak about 12 hours later was reported. Our results seemed to concur with the consensus that ethnic differences or age considerations play little or no part in the onset of occurrence of myocardial infarction. Physiological variations probably account for most part, when a person develops an acute ischaemic syndrome.

A recent and elegant report by Muller et al from the MILIS (Multicenter Investigation of the Limitation of Infarct Size) study data base, also showed objectively the circadian variation in the onset of myocardial infarction. Here, the time of onset was based on the construction of the CK-MB (MB fraction of the creatine kinase) curves. This method obviously entailed the repeated sampling of blood from patients at frequent intervals so as to determine the peak
The peaking of the CK-MB fraction has been demonstrated to predict fairly accurately the onset of myocardial infarction some 20–24 hours earlier. Whilst this method is obviously rigorous and precise, it also has the disadvantage of knowing the onset of infarction only after extrapolating from the CK-MB curve, i.e. some delay in 24 to 48 hours.

Why there is this circadian variation in acute myocardial infarction is not clear. Whilst it is easy to isolate various factors which seem to follow a temporal pattern, it is more difficult to determine how they all act in concert to produce the syndrome of myocardial ischaemia or infarction in particular. We do know however, that cortisol, catecholamines, blood pressure and heart rate peak in the early morning hours. These may further interact with the environmental factors of stress and arousal. Such enhanced sympathetic activity on the heart may make even greater demands on myocardial oxygen consumption and oxygen uptake, particularly when underlying atherosclerotic vascular disease is present. Critical narrowing of atheromatous coronary arteries can easily be tipped over to total occlusion either by vasospasm or by thrombus formation over a ruptured plaque.

To aggravate the situation, haemorrheological factors such as heightened platelet aggregability and diminished fibrinolytic activity only predispose further the tendency towards coronary thrombosis, hence acute myocardial infarction. The explanation for the secondary peak is presently speculative and conjectural.

Whilst our survey method may be criticised from the viewpoint that subjective admission of typical infarct symptoms is less than totally accurate, it nevertheless has its merits in clinical practice. Most infarct patients can remember the onset well especially when the symptoms are well-defined i.e. catastrophic central chest pain associated with sweating (68.2%), sensation of dyspnoea associated with severe chest constriction (8.8%). Often, they can pin-point their onset to within the half hour or hour, especially so when they are woken from sleep or disturbed from work or activity. Not so precise would be those who present with dyspnoea from heart failure secondary to a silent infarct.

Those presenting with acute pulmonary oedema secondary to infarction, (some 13.2%) often arrive at hospital in a state of acute respiratory failure where documentation of their onset of symptoms would be fairly precise. Those presenting with cardiovascular collapse (9.8%) also may give a fair estimate of their onset of symptoms, though for obvious reasons, not all could. One major weakness in our study was the inavailability of data from 104 patients (24.6%). This was in part due to poor data collection, patients transferring in from various other wards, and collapsed patients who died subsequently without substantial recovery to enable accurate taking of history of symptoms.

In several studies where thrombolytic revascularisations were used to prospectively treat acute myocardial infarction, the onset of symptoms were also taken to be the onset of myocardial infarction. In the GISSI study, those who presented within three hours and three–six hours were 51.5% and 31.5% respectively. In these two crucial groups, revascularisation rates were higher. The ISAM study also had similar statistics i.e. 42% and 38% respectively.

We highlighted the time delay in getting to the hospital as this factor has become increasingly important in determining which patient might benefit from early aggressive therapy, including thrombolysis. The GISSI study and others have shown that the earlier thrombolytic therapy is commenced, the greater the chances of revascularisation and myocardial salvage. In particular, those presenting within four hours of the onset of acute myocardial infarction.
would benefit most. Thus from our study, 56.8% of our patients may benefit from this accepted mode of therapy. If six hours, is taken as the cut-off point where thrombolysis can be considered, then as many as 71% may benefit.

This, of course, excluded the group of 104 (24.6%) whose data were not analysable. Here some 40.4% (42) died suddenly soon after admission, but whose electrocardiographic and enzymatic results met the criteria for myocardial infarction. Another group which inevitably escapes analysis, is that group which failed to present to the hospital at all, or died before being able to (sudden cardiac death). This group, in any community would form as many as 50% of all true myocardial infarctions.

Notwithstanding the above limitations, our data has shown that the Malaysian population exhibits a similar circadian variation in the onset of acute myocardial infarction, as well as a similar delay in getting medical assistance from the hospital. About 71% presented within six hours of their presenting symptoms and may benefit from the current modern practice of thrombolytic therapy. Even if one were to be more conservative, and treat only those who present within four hours, some 56.8% may actually benefit. For General Hospital Kuala Lumpur alone, the cost of such therapy may be prohibitive. For the annual 600 or so cases of acute myocardial infarction, some 350 patients qualify for thrombolytic therapy by presenting within four hours. At about M$600 per dose of 1.5 megaU of streptokinase, the annual budget would need an additional M$210,000 (excluding other incidental costs)! When one considers tissue plasminogen activator (t-PA), the cost becomes even more staggering, at US$2000 per dose! Perhaps, this is not too big a price to pay for improved cardiovascular morbidity and prognosis. Recently data are becoming available which not only projected savings in terms of recurrent cardiac events, complications from poor myocardial function due to excessive ischaemic loss but also in economic terms. Patients may be able to return back to home and occupation sooner — shorter hospitalisation and rehabilitation — even fewer relapses. Thus in the long-term, successful thrombolytic revascularisations may be much more economical.

To conclude, we urge that the public and medical practitioner be made even more cognizant of the early symptom presenting features of acute myocardial infarction and seek prompt hospitalisation so as to secure the best results and benefit, with or without thrombolytic therapy.

Acknowledgements

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