Circadian, circaseptan and circannual periodicity of cardiac arrest

In this issue, Arntz and colleagues published an interesting report on the daily (circadian), weekly (circaseptan) and monthly (circannual) variation in the occurrence of sudden death in West Berlin during the 5-year period from 1987 to 1991[1]. The city of West Berlin, with about 2 million inhabitants, offered a unique opportunity of studying a population that was clearly defined within ‘the Wall’. Moreover, this population remained nearly constant on a day-to-day basis because of the almost complete absence of ‘noise’ produced by commuters to and from the study area.

During this 5 year period, demographic data were collected prospectively on 24,061 consecutive cases of cardiac arrest of presumed cardiac origin attended by the West Berlin emergency medical services. The authors estimated that the figure of approximately 5000 events per year represents about 50% of all sudden deaths of presumed cardiac origin[2]. This amounts to an annual incidence of 10,000 sudden deaths of presumed cardiac origin, corresponding to an incidence of five per 1000 inhabitants per year. According to the authors, this surprisingly high figure is probably related to the unusually elderly age profile of the population. The figure contrasts with the data from MONICA, in which three German collaborative centres had an annual incidence of heart attacks ranging from 276 to 376 per 100,000 for males and from 49 to 78 per 100,000 for females. Certainly, there are differences between the MONICA and the Berlin study populations; in MONICA there is an age limit for inclusion in the database of 65 years, whereas in Berlin there is no age limit. Assuming an observed case fatality rate of 50%, with 60% of deaths occurring outside the hospital, the figure of sudden death of presumed cardiac origin obtained in Berlin remains high. The chronobiological data of this unusual study population are supported, however, by extensive literature from other parts in the world. No data are reported on the resuscitation efforts and on eventual outcome. We look forward to learning more of these matters in a future report.

One major but unavoidably weak element in the study is that the time of the occurrence of the cardiac arrest was taken vicariously as the time of the emergency call to the emergency medical services. This probably provides the best and most reliable estimate of the time of occurrence of the cardiac arrest, but the reader should not forget that it is an extrapolation. The study confirmed the well-known biphasic circadian variation of emergency calls for sudden death, with a first morning peak some 3 to 6 h after awakening and a second but smaller peak in late afternoon. In the present study, the timing of the morning peak also seemed to be clearly modulated by factors that influence the time of awakening, such as the day of the week, age and sex of the victim, the season, and also by other external factors such as working hours, weekend activities, temperature, and summer holidays.

In the past 15 years, Arntz and his colleagues have been amongst those who have contributed extensively to the scientific literature relating to chronobiology of acute cardiovascular events. This daily variation has been reported for different regions in America and Europe using a variety of methods. A Medline search revealed at least 150 well documented articles published since 1985 relating to the subject ‘sudden death or cardiac arrest’ and ‘circadian or diurnal or weekly or seasonal variation’. An impressive number of papers have demonstrated clearly the circadian variation in the occurrence of acute cardiovascular events such as myocardial ischaemia, myocardial infarction, ventricular arrhythmias, cardiac arrest, and thrombotic stroke. Similarly, numerous published studies have reported on the circadian variation in underlying biological variables. The pathophysiological hypothesis, that vulnerability in the vascular substrate leads to an acute event as a result of haemodynamic, vasoconstrictive and prothrombotic forces, has been supported by many investigators.
The mechanism of initiation of ventricular fibrillation is one example of a complication that may follow when the abnormal substrate becomes more vulnerable and is subjected to a triggering event. It shows a similar circadian rhythm to that of all acute ischaemic events with a relatively higher risk during daytime and the highest peak in the first 3–6 h after awakening.

The substrate is usually an unstable atherosclerotic plaque. Other types of pathological substrate are ventricular hypertrophy, dilatation, myopathy, and congenital abnormalities. In the minority of cases, no pathological substrate can be found.

The substrate becomes increasingly vulnerable in the hours after awakening as a result of increased sympathetic activity. This, together with augmented responsiveness to catecholamines, leads to an elevated vascular tone and vasoconstriction. An increase in myocardial oxygen consumption also occurs as a result of increased blood pressure and heart rate. Protective vagal tone is decreased. Emotional and physical stress, upright position, and heart rate. Protective vagal tone is decreased. Gastrointestinal mias. In the minority of cases, no pathological substrate can be found.

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The final trigger is usually early ventricular premature depolarizations. The co-existence of ventricular premature depolarizations, decreased electrical stability, latent pacemaker activity and abnormal propagation of the impulse (as a result of brady-cardia, intraventricular conduction blocks, intramural re-entry phenomena) generate chaotic electrical activity in the presence of a lowered fibrillation threshold. Once this disorganization spreads to a critical mass of ventricular myocardium, fibrillation invades the whole ventricle causing ventricular fibrillation. The pro-arrhythmogenicity of myocardial ischaemia or infarction is well understood. Combined with an early morning decrease of heart rate variability and prolongation of the QT interval, the ingredients of a deadly cocktail are brought together, with ventricular fibrillation and cardiac arrest as the well-known consequences.

Technology has provided us with exciting tools allowing us to study these variables. Relatively ‘soft’ data, such as death certificates and records of emergency medical services interventions, are now supported by ‘hard’ data provided by continuous recordings of the heart rate and rhythm, of the ST and the QT segment, and of blood pressure. These Holter type methods are of high value in documenting the chronobiology of physiological parameters and ischaemic events that trigger arrhythmic events leading to cardiac arrest. Even more recently, the memory facility of implanted defibrillators has provided additional evidence in support of the increased incidence of ventricular premature depolarization, ventricular tachycardia and ventricular fibrillation. Electronic rhythm history of implanted defibrillators and Holter recordings of patients who died suddenly confirm that more than 80% of cases of sudden cardiac death are due to ventricular tachyarrhythmias. In the initiation of ventricular fibrillation, a so-called ‘R on T’ extrasystole is a most important factor. Frequently a period of ventricular tachycardia precedes the degeneration of this rhythm into ventricular fibrillation. A late cycle, ectopic and idio-ventricular rhythm, initiate ventricular fibrillation less frequently. An interesting side product of these methods was the identification of decreased heart rate variability as a marker of an imbalance in the autonomic nervous system.

Now that an impressive amount of convincing evidence is available that confirms the circadian, circaseptan, and circannual variability of myocardial ischaemia, infarction, and cardiac arrest, the question arises as to how this evidence can be applied to clinical practice, especially in regard to the design of appropriate therapeutic intervention trials. We have the possibility of identifying the individuals at risk for ischaemic heart disease. We have probate methods, such as heart rate variability, to identify patients at increased risk for malignant arrhythmias. We know that beta-blocking agents and possibly also some calcium antagonists may blunt the morning peak in heart rate and blood pressure. We know the beneficial effect of aspirin on thrombogenicity. We have good technological tools for documenting heart rate and rhythm, blood pressure and myocardial ischaemia.

Is it not time to consider a therapeutic intervention trial in patients with increased potential for sudden cardiac death?

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Concerning gender and therapy after acute myocardial infarction: are there differences between men and women?

See page 284 for the article to which this Editorial refers

Since the time of the ancient Greeks — and probably before that time as well — men and women have debated and discussed the differences between the genders. As the new millennium dawns, societal distinctions between the sexes seem to be waning in many countries: a large number of women have achieved parity or near parity with men in their professional lives, although some wage disparities still exist. With respect to short- and long-term gender prognosis following acute myocardial infarction, considerable disagreement continues to exist. Most trials have shown that unadjusted mortality is higher in women than in men. However, female patients with myocardial infarction are on average older, more diabetic and hypertensive, and demonstrate a higher number of co-morbid conditions than is the case for male patients. Despite careful statistical analysis, with correction for underlying age and co-morbid conditions, some studies still report higher short- and long-term mortality for women post myocardial infarction while other investigations show no substantial gender difference[1–8].

In this issue, Gottlieb et al.[9] report on short- and long-term mortality in nearly 8000 patients with acute myocardial infarction. These individuals come from two comparable registries — one recorded during 1981–1983 and the second during 1992–1994. Three-quarters of the patients in each registry were men. Thirty-day and 1-year mortality rates declined substantially for both genders between the two time periods studied, although age-adjusted (but not co-morbidity adjusted) 30-day and 1-year mortality rates were both higher for women than for men. The authors attribute the decline in mortality to the ‘implementation in daily practice of new therapeutic modalities’, e.g. thrombolysis, coronary angiography, angioplasty and coronary bypass surgery. All of these diagnostic and therapeutic interventions increased substantially between 1981–83 and 1992–94.

However, other factors might have contributed to the observed decline in mortality between these two time periods. Considerably more patients were receiving beta-blockers, ACE inhibitors, aspirin and nitrates during 1992–94 than during 1981–83. In addition, more sensitive biomarkers for infarction were undoubtedly employed in some centres during 1992–94 thereby identifying small infarcts that would have been overlooked in 1981–83. Small infarcts have better short-term prognosis compared with large infarcts. Despite this latter confounder, it is almost certain that the prognosis for myocardial infarction has improved over recent decades in part as a result of better therapy and in part as a result of increasingly widespread secondary preventive measures.

But what are we to make of the gender differences which continue to be reported in large series of post-myocardial infarction patients? Not only are there gender differences in mortality and morbidity, but also discrepancies exist in the rate of therapeutic interventions between genders. Indeed, this was the case in the report of Gottlieb et al.[9] in this issue in...