Circadian variation of arrhythmic events, electrophysiological properties, and the autonomic nervous system

See page 2192, doi:10.1053/euhj.2001.2677 for the article to which this Editorial refers

Malignant ventricular tachyarrhythmias and sudden cardiac death exhibit a circadian variation with a distinct peak during morning hours[1,2]. The underlying cause for this observation appears to be complex and multifactorial. For example, in a field study in patients with out-of-hospital cardiac arrest, Arntz and co-workers[3] found a clear diurnal variation in patients with ventricular fibrillation but not in patients with asystole. A better understanding of the triggering factors leading to the initiation of arrhythmias has therefore been a major task in order to find strategies to prevent such catastrophic events. Myocardial ischaemia, as a well known trigger for arrhythmias, has been suggested as a major cause since ischaemia-related conditions such as anginal attacks, myocardial infarction and stroke have been found to occur more frequently during morning hours as well[4]. This may be due to various factors exhibiting a similar diurnal variation, i.e. a morning surge in sympathetic activity and an increase in catecholamine levels, elevated blood pressure, increased platelet aggregability, and diurnal variations in endothelial function. In addition, external factors such as strenuous physical activity and emotional stress have also been found to play a role in the initiation of ventricular arrhythmias[5]. However, despite the fact that all these factors may lead to myocardial ischaemia, the diurnal distribution of malignant arrhythmias is not different in a patient with versus without ischaemic heart disease[6], suggesting the importance of other factors as well.

Previous studies have shown a diurnal variation in electrophysiological properties. For example, the QT interval exhibits a circadian variation, with a longer corrected QT interval during sleep than during waking hours[7]. Furthermore, the dispersion of the corrected QT intervals is greater during daytime than during sleep[8]. These parameters indirectly reflect measures of ventricular action potential duration and repolarization, which are both important determinants for the genesis of arrhythmias. Another parameter more directly reflecting repolarization characteristics is ventricular refractoriness. Ventricular refractoriness has been determined invasively[9] and non-invasively (using the telemetry function of implanted pacemakers[10,11]) and has been found to be shorter during daytime and longest during sleep. In one study[11], the time of day was the only independent predictor of ventricular refractory periods, and ventricular refractory periods were shortest around the hour of awakening, i.e. at a time when the incidence of sudden death has been found to be highest[12]. Thus, a circadian variation in electrophysiological properties may play a significant role in the complex pathogenesis of arrhythmia initiation and sudden cardiac death.

Beta-blockade eliminates the diurnal variation of ventricular refractory periods, although there is no clear relationship between ventricular refractoriness and plasma catecholamine levels[11]. This suggests that fluctuations in sympathetic nervous activity (which does not directly correlate with plasma norepinephrine concentrations) may be responsible for these observations. In this issue, Simantirakis et al.[13] investigated the relationship between the circadian variation of refractory periods and autonomic nervous system activity. They studied patients with primary conduction disease and without overt heart disease who had been chronically paced after permanent DDD pacemaker implantation. Using the pacemaker programming capabilities they measured both the atrial and ventricular refractory periods at two different cycle lengths bi-hourly over 24 h and correlated these findings with spectral indexes of heart rate variability as a marker of increased sympathetic or parasympathetic tone.

The authors could reproduce the previously reported findings of a circadian variation for atrial and ventricular refractory periods, with longer refractory periods during the night (when patients are asleep) and shorter refractory periods during the day[13]. The new finding in the study is that there is a clear relationship between the autonomic tone and the circadian variation of the refractory periods. Atrial and ventricular refractory periods are shorter during periods of high sympathetic tone (indicated by the high power of the low frequency band (LF)), i.e. during daytime, and substantially lengthen during periods of high parasympathetic tone (indicated by
the high power of the high frequency band (HF)), i.e. during the night. Thus, the higher the sympathetic or parasympathetic activity of the autonomic nervous system, the shorter or longer are the refractory periods, respectively. This relationship is also expressed as a strong negative correlation between atrial and ventricular refractory periods and the ratio of the spectral power of the low and high frequency band (LF/HF), which was used as a measure of the sympathovagal balance of the autonomic nervous system.

The study population was small and comprised of patients with sick sinus syndrome (n=13) and complete heart block (n=11). When groups were analysed separately the authors found longer atrial refractory periods in patients with sick sinus syndrome than in patients with complete heart block. In contrast, ventricular refractory periods were longer in patients with complete heart block than in patients with sick sinus syndrome. This is an interesting finding which, to our knowledge, has not been described previously. The most striking difference between the two groups is that patients with sick sinus syndrome had almost always been paced in the atria (97% ± 9% of the time since pacemaker implantation) but not in the ventricles, whereas patients with complete heart block had almost always been paced in the ventricles (98% ± 5% of the time) but not in the atria. This observation could suggest that chronic stimulation may have some influence on myocardial refractoriness (in the atria or ventricles). However, methodological reasons may be responsible, too. Steady state adaptation of action potential duration (which closely parallels refractoriness) may take up to several minutes after abrupt cycle length changes.[14]. Simantirakis et al.[13] did not report the heart rate of patients prior to the electrophysiological measurements. The heart rate in the two groups could have been different since patients with sick sinus syndrome were paced at a fixed heart rate of 60/min whereas patients with complete heart block were programmed at DDD 35/min, allowing lower heart rates than the group with sick sinus syndrome (especially during the night). Thus, the magnitude of cycle length changes to the drive cycle length of 600 or 500 ms used for the determination of the refractory periods could have been different in the two groups thereby possibly affecting the adaptation of action potential duration and refractoriness.

Heart rate variability parameters could be determined only in those patients with complete heart block since patients with sick sinus syndrome were almost continuously paced in the atrium. Nevertheless, the findings by Simantirakis et al.[13] highlight the relationship between electrophysiological properties and autonomic control of the heart. The results may — at least in part — explain why supraventricular and ventricular tachyarrhythmias occur more often during daytime since short refractory periods may promote the initiation of reentrant circuits within the myocardium, facilitating the induction of atrial or ventricular fibrillation in high risk patients. Furthermore, the results may explain why beta-blocker therapy interacts with the circadian variation of electrophysiological properties,[11], possibly leading to a suppression of the morning peak of malignant arrhythmias[15] and sudden cardiac death[16]. However, there are questions left unanswered. Since patients in the study by Simantirakis et al.[13] had no overt coronary or other structural heart disease the influence of various underlying cardiac diseases on the relationship between refractory periods and autonomic nervous system activity remains unclear. In addition, it is not clear whether and to what extent the circadian variation of refractory periods is modified in patients with autonomic nervous system dysfunction (i.e. patients with diabetes mellitus) who are known to have an increased risk of arrhythmia development. Thus, further studies in these patient populations are important to better understand the underlying mechanisms of the circadian variation of electrophysiological properties in patients at risk, and to develop further strategies to interact with this unfavourable profile during morning hours.

References

Coronary artery bypass graft (CABG) surgery is the most frequently performed cardiac surgical operation. Excellent conduit is a vital ingredient, and meticulous surgical technique is crucial. Unfortunately the perfect conduit for CABG is not available. The following criteria have been suggested. The conduit should be easily available in adequate quantity. Harvesting should entail no morbidity. It should not suffer rejection, degeneration or stenosis. It should be cheap. It should have excellent flow characteristics and not be affected in an adverse way by endogenous or exogenous factors. Well established options include the long and short saphenous vein and internal thoracic artery. The internal thoracic artery in particular is resistant to atherosclerosis with excellent long-term patency\(^1,2\) even when re-used. Other conduits for which there is variable use are the cephalic vein, radial, gastroepiploic and inferior epigastric arteries. Carpenter first reported use of the radial artery in CABG in 1973\(^3\). Initial optimism was dampened by the effects of vasoconstriction and high early occlusion rates. Over the last decade the technique has been refined with the artery being gently harvested with its surrounding fascia and veins, minimal iatrogenic distension and the use of pharmacological vasodilators\(^4\). With these modifications the radial artery has been shown to have an angiographic patency rate of 83% at 5 years\(^5\).

Advantages associated with the radial artery also include harvest from a site which has good collateral blood supply and nervous innervation and a more favourable microbiological environment than the leg. As a consequence the radial harvest site is less prone to infection, neurological injury, delayed healing and prolonged oedema than the saphenous vein. There is also increasing experience of its use in the elderly, a group in which it may have a satisfactory safety profile and in whom there is often a shortage of other conduit. In addition it appears to share some of the prognostic advantages associated with the internal thoracic artery\(^6\). As disadvantages it can only be used as a free graft, and as an artery with a high muscle to elastic ratio and alpha adrenoceptor function\(^6\) is prone to spasm, which may have serious consequences particularly in the early postoperative period. Therefore the paper by Harrison \textit{et al.} in this issue is a welcome investigation of radial artery optimisation for CABG\(^7\).

In current surgical practice it is well established to use vasodilators peri-operatively in the preparation of conduit and these may be applied topically or endoluminally or both. Popular choices include papaverine, verapamil and to a lesser extent sodium nitroprusside and phenoxybenzamine. Vasodilators may be used at the time of harvesting, for a brief period between harvesting and implantation, and

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**References**