Late potentials, ventricular arrhythmias and intervention.
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Chapter 11

Summary

Acute myocardial infarction is a very serious disease. In the acute phase, it causes a considerable mortality, and during the subsequent year after discharge another 4–10% of the patients die. Over the last three decades, mortality in the acute phase is decreased (partly due to the introduction of the coronary care unit in hospitals), but unfortunately the mortality in the first year after discharge from the hospital is hardly decreased. This so-called late mortality is caused by recurrent myocardial infarction, congestive heart failure, and ventricular arrhythmias. The latter are the cause of sudden, unexpected death and are the most important cause of this late mortality. Because of the unexpected occurrence of such arrhythmias, much research was performed in order to identify harbingers of these ventricular arrhythmias. The identification of such harbingers is of tremendous importance because it theoretically enables to install preventive treatment in patients with a high risk of sudden death, because, once these arrhythmias occur, treatment is usually too late. One of those harbingers are late potentials that can be detected by means of signal-averaging of the body surface electrocardiogram.

In this thesis the incidence and predictive value of late potentials was studied in various conditions in the pig and in man. Furthermore, the effect of interventions on late potentials was investigated. A review of the recent literature in relation to the studies described in this thesis is presented in Chapter 1.

Late Potentials as Indicators of a Substrate for Ventricular Arrhythmias

In Chapter 2 a porcine model of ischemia and reperfusion is presented. Late potentials were shown to develop after myocardial infarction, and their relation to inducible ventricular tachycardia was comparable to that in man, but clearly different from that in dogs. Moreover, the absence of collateral coronary circulation makes the porcine heart a feasible model for intervention studies mimicking thrombolysis in man.

The predictive value of late potentials in man for arrhythmic events after myocardial infarction is discussed in Chapter 3. The data corroborate the view that late potentials are harbingers of arrhythmic events. This predictive value is not higher in the presence of QTc prolongation at the twelve lead electrocardiogram. Thus, whereas other investigators reported a higher risk of arrhythmic events when late potentials and a low ejection fraction (< 40%) or complex ventricular arrhythmias are simultaneously present, the results of our study do not indicate that the presence of concomitant QTc prolongation should raise extra concern.
In Chapter 4 we describe a new congenital long QT syndrome, characterized by QTc prolongation at low heart rates. We call this a bradycardia-dependent long QT syndrome, in contrast to the adrenergic-dependent long QT syndromes (such as the Romano-Ward syndrome) in which QTc prolongation is present at high heart rates. In spite of a disconcertingly high incidence of sudden death in this family, previously we never found any clues pointing toward a higher susceptibility to arrhythmias in these subjects. However, a very high incidence of late potentials was found in subjects with the syndrome. Late potentials may be adjuncts in both the detection and in the risk stratification of patients with the syndrome.

The results of the studies described in this section of the thesis show that late potentials are markers of arrhythmic events after myocardial infarction, and that they are also present in other heart diseases. These heart diseases, although rare, become more important in view of the increasing sporting activities in the population with a concomitant increase in sudden death during exercise. The value of late potentials, both for diagnostical purposes and in terms of risk stratification in heart diseases other than myocardial infarction has at present not been studied to a sufficient extent. This issue needs to be addressed in prospective studies.

Treatment Strategies that Reduce the Incidence of Late Potentials After Myocardial Infarction

Angiotensin converting enzyme (ACE) inhibitors are increasingly administered to patients who suffer from an acute myocardial infarction, shortly after the event. Animal studies have shown that the administration of ACE inhibitors during ischemia and reperfusion will render the myocardium less sensitive for ventricular arrhythmias during the first two weeks after the event. Both animal and human data show that (early) administration may also influence the remodeling process of the damaged myocardium, i.e. modulate the substrate development.

The ACE inhibitor perindopril, when administered during ischemia and reperfusion in pigs and during the subsequent days, significantly improved survival. Furthermore, ACE inhibition appeared to prevent the development of late potentials (Chapter 5).

One of the effects of ACE inhibition is enhancement of endogenous bradykinin levels, and in Chapter 6 we showed that bradykinin infusion during ischemia and reperfusion in pigs also prevents the development of late potentials. Therefore, potentiation of endogenous bradykinin partly explains the mechanism of action of ACE inhibition.

Apart from these subchronic effects, ACE inhibition may have an acute effect on inducible or spontaneous ventricular arrhythmias. Similarly, it was shown in Chapter 7 that bradykinin affects the inducibility of ventricular tachycardia. This partly explains the beneficial effect of perindopril as described in Chapter 5.

Another treatment strategy that might reduce the incidence of late potentials after acute myocardial infarction is pharmacological reperfusion. Thrombolysis-induced patency of the infarcted coronary artery is associated with a reduced incidence of late potentials as harbingers of life-threatening arrhythmic events. Larger studies and other studies are needed to confirm these results.

The results of these experiments were the reason for the administration of thrombolysis regimens in the present study. However, the trend toward a reduction of late potentials during thrombolytic therapy was not statistically significant.

The present study is the first to report that a significant trend toward a reduction of late potentials after myocardial infarction is influenced by improved survival. Further research is mandatory to establish an adequate and safe reperfusion strategy and to reduce the incidence of late potentials.
Late Potentials

administered to patients. Animal experiments during ischemia and reperfusion showed that late potentials during ischemia and reperfusion were reduced survival. Furthermore, late potentials (Chapter 3) were shown to have an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival. Therefore, potential to lower an acute effect on survival.