Original Article

Assessment, Significance and Mechanism of Ventricular Electrical Instability after Myocardial Infarction

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The mechanism of reentrant tachycardia was established nearly a century ago, but the relationships between myocardial infarction and predisposition to sudden death were not unravelled until much later. In the latter half of the twentieth century many studies sought to ascertain what variables were predictive of death following myocardial infarction. Approximately one half of all deaths during the year following myocardial infarction are sudden and due to ventricular tachycardia (VT) or ventricular fibrillation (VF). We aimed to utilise non-invasive signal-averaging, along with programmed electrical stimulation of the heart, to determine whether one could predict spontaneous ventricular tachycardia and sudden death late after myocardial infarction. The sensitivity of ventricular electrical instablility (inducible ventricular tachycardia or fibrillation) as a predictor of instantaneous death or spontaneous VT was 86%, and the specificity was 83%. When other variables (delayed ventricular activation at signal-averaging, ejection fraction at gated heart pool scan, ventricular ectopic activity at ambulatory monitoring and exercise testing) were taken into account, inducible VT at electrophysiological study was the single best predictor of spontaneous VT and sudden cardiac death after myocardial infarction. The Westmead studies of Uther et al. in the decade or so from 1980 established programmed stimulation as the best predictor of sudden death after myocardial infarction. Subsequent studies by others have demonstrated a survival advantage of defibrillator implantation in patients with low ejection fraction (and inducible ventricular tachycardia) after myocardial infarction.

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Assessment of Prognosis after Acute Myocardial Infarction Prior to 1980

The mechanism of reentrant tachycardia was established nearly a century ago,[1] but the relationships between myocardial infarction and predisposition to sudden death were not unravelled until much later. Sir James Mackenzie[2] noted that, 'Extrasystoles in themselves are not signs of any specific injury to the heart, nor should a prognosis of any gravity be based on their appearance alone'.

Early last century little was known about the aetiology of myocardial infarction or of sudden death. In 1913 Mackenzie[3] wrote, 'There are cases in which angina pectoris develops with great severity and ends speedily with death. On the whole, these cases are rare'. In 1945 Samuel Levine described a patient with recent myocardial infarction who died suddenly in ventricular fibrillation:[4] 'This patient had previous angina and had had a recent acute myocardial infarct. He was doing quite well and just after the first lead of the electrocardiogram was taken he expired. Leads II and III, taken only a few seconds afterwards, showed that ventricular fibrillation was present.'

Predictors of Death after Myocardial Infarction

In the latter half of the twentieth century many studies sought to ascertain what variables were predictive of death following myocardial infarction. Older patients with left ventricular failure and previous myocardial infarction fared less well than younger patients without left ventricular failure or previous myocardial infarction.[5–7] A poor prognosis following myocardial infarction was also associated with persistent ST segment displacement,[8] persistent sinus tachycardia,[9] left ventricular dysfunction assessed by ejection fraction[10,11] or elevation of left ventricular end diastolic pressure[11] and severity of coronary artery stenoses.[11,12] Notwithstanding Mackenzie's previous view to the contrary, a poor prognosis was also associated with complex ventricular premature beats.[13–15]

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It was known that death following myocardial infarction may be due to progression of coronary artery stenoses and reinfarction. This may apply particularly in patients who survive nontransmural myocardial infarction.[16,17] However, overall mortality rates following nontransmural compared with transmural infarction appeared similar.[18–20] Thus, the prognosis following transmural and nontransmural infarction depends on several factors including size of initial infarction, subsequent left ventricular dysfunction, further ischaemic episodes and occurrence of spontaneous ventricular tachycardia (VT) or ventricular fibrillation (VF). Significant progression of coronary arterial stenoses may be detected by serial exercise testing.[21–23] However, predisposition to spontaneous VT, VF and sudden death is not necessarily related to another ischaemic event.[24]

Predictors of Sudden Death after Myocardial Infarction

Approximately one half of all deaths during the year following myocardial infarction are sudden[5,7,11,25–29] and due to VT or VF.[30] However, patients who die suddenly do not comprise a homogeneous group. Some patients die rapidly in VT or VF associated with acute ischaemia (with or without reinfarction) whereas others die virtually instantaneously following the onset of spontaneous VT or VF without any clinical or post mortem evidence of fresh infarction.[24]

Kannel et al.[31] found that the risk of sudden death (death within one hour of onset of symptoms) was positively correlated with hypertension, left ventricular hypertrophy, obesity and cigarette smoking. However, these authors were unable to distinguish between individuals at risk of sudden death and others at risk of non-sudden death from myocardial infarction. In another study, Doyle et al.[32] found that suddenness (speed of onset) of death was unrelated to serum cholesterol concentration, systolic blood pressure, relative body weight, cigarette smoking, electrocardiographic evidence of left ventricular hypertrophy, age and previous coronary heart disease. Norris et al.[6] noted that sudden death could not be predicted on the basis of age, left ventricular failure or previous infarction. Moss et al. [29] found no correlation between complexity of spontaneous ventricular ectopic beats and suddenness of death.

Numerous studies[33–41] addressed the efficacy of different therapeutic regimens to prevent sudden death. All of these studies, which had addressed the problem of coronary artery disease per se (pathogenesis and complications of atherosclerosis) and or the problems of spontaneous VT and VF, utilised treatment of heterogeneous groups of patients including some with, and some without, a predisposition to reinfarction, and some without a predisposition to spontaneous VT or VF in the absence of reinfarction.

In retrospect, it was obvious that prevention of myocardial ischaemia was unlikely to benefit patients with a predisposition to spontaneous VT or VF (in the absence of reinfarction or acute ischaemia). Equally, therapy aimed at prevention of spontaneous VT and VF would be unlikely to benefit patients with a predisposition to VT and VF associated with acute ischaemia. The latter patients could be identified by serial exercise testing and coronary angiography. In 1979, John Uther understood clearly these principles, and planned to test his ideas.

The Background to Electrophysiological Investigation at Westmead Hospital

While working at Royal Prince Alfred Hospital in Camperdown, Uther was the first to establish medical and surgical electophysiological programs in Sydney. He had previously utilised indicator dilution techniques to quantify valvular regurgitation, as a BSc(Med) student of Professor Paul Korner. He subsequently completed a doctor of medicine degree, studying the central nervous integration of cardiovascular reflex responses to arterial hypoxia, again with Korner.

In 1970 with Professor Arthur Guyton in Mississippi, Uther developed computer models using finite element analysis to study physiological control systems. In 1971, at the laboratories of Professor Eugene Braunwald at the University of California San Diego, Uther developed Fortran programs to allow signal-averaging of data from intravascular electromagnetic flow meters. The accuracy of signal-averaging was then validated against periaortic electromagnetic flow meters in acute animal experiments. In 1972, together with Dr. John Chalmers, Dr. David Tiller, and Dr. John Horvath, Uther established a hypertension clinic at Royal Prince Alfred Hospital. Then, with Dr. Andrew Tonkin and Dr. Malcolm West, Uther utilised right heart catheterisation and thermodilution techniques to study the sensitivity of the baroreflex system, using progressive autonomic blockade with atropine, propranolol, guanethidine and phentolamine infusions, and bolus injections of nitroglycerine and neosynephrine in hypertensive patients and controls.

In 1974, with Dr. Joe Hung, Uther studied sources of variation of His-Purkinje conduction time. With his colleagues Dr. Grayson Geary and Dr. Norman Sadick (who would later serve with Uther as consultant cardiologists at Westmead) he reported with Dr. Douglas Baird (cardiothoracic surgeon) his early Australian experience with electrophysiological assessment and surgical treatment for supraventricular tachycardia.[42] Uther developed a Frank vectorcardiogram[43] signal-averaging system to identify delayed ventricular activation non-invasively during sinus rhythm in patients prone to spontaneous ventricular tachycardia.[44]

In 1979, Uther moved from Royal Prince Alfred Hospital (near the central business district of Sydney), to head cardiology at the recently commissioned Westmead Hospital (near the demographic centre of greater Sydney). In his new position as head of a cardiology unit with a catchment of 1.6 million inhabitants, he proposed a study of sudden death in patients with ischaemic heart disease. His aim was to utilise non-invasive signal-averaging, along with programmed electrical stimulation of the heart, to determine whether one could predict ventricular electrical instability