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Role of Implantable Cardioverter Defibrillators for Dialysis Patients

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1. Introduction

The number of patients suffering from chronic kidney disease (CKD) and end-stage renal disease (ESRD) is increasing worldwide (Ansell et al., 2007; National Institutes of Health, 2009). Mortality is high with cardiac disease being the primary cause of death, especially in long-term dialysis patients (84.5 per 1000 patient years) (National Institutes of Health, 2009). Yearly mortality is ~4% in dialysis patients younger than 20 years but rises gradually to 35% in patients older than 65 years. Ventricular arrhythmias account for >60% of all sudden cardiac deaths (SCD) (Bleyer et al., 2006; Eknoyan et al., 2002; Wanner et al., 2005). A retrospective analysis of the Multicenter Automatic Defibrillator Implantation Trial showed a correlation between renal function and risk of SCD (Goldenberg et al., 2006). For each 10 unit reduction in estimated glomerular filtration rate (eGFR), the risk of all-cause mortality and SCD increased by 16% and 17%, respectively.
Outcome after a cardiac arrest is poor. Most dialysis patients die immediately or within 30 days after a cardiac arrest (Herzog et al., 2005). Measures aimed at modifying risk factors and preventing this catastrophic outcome are urgently needed (De Bie et al., 2009; Passman et al., 2011; Young, 2011).

2. Risk factors for sudden cardiac death

In the general population, ischaemic heart disease and moderate to severe left ventricular systolic dysfunction are the major risk factors for SCD (National Institutes of Health, 2009). CKD patients often suffer from significant cardiovascular morbidity (hypertension, diabetes, vascular disease). However, the exact pathophysiology of SCD in dialysis patients is not fully understood and includes risk factors specifically related to end-stage renal disease. Left ventricular hypertrophy (LVH) is one potential factor. It is very common in dialysis patients and often accompanied by microvascular disease and marked interstitial fibrosis which is more pronounced than in non-renal patients with similar degrees of LVH (Amann et al., 1998). Other cardiac abnormalities associated with CKD are functional and structural changes of intramyocardial arteries, reduced capillary density and abnormalities of myocardial metabolism leading to reduced myocardial perfusion reserve (Amann & Ritz, 1997). Increased sympathetic activity has also been identified as a cause for the increased risk of SCD (Nishimura et al., 2010). Recent hospitalization, malnutrition, inflammatatory processes and use of catheter for dialysis access are also markers of increased risk (Pun et al., 2011).

Several studies have reported a temporal relationship between SCD and the haemodialysis procedure (Bleyer et al., 2006; Karnik et al., 2001; Pun et al., 2011). Reports suggest that 20-30% of dialysis treatments are complicated by intradialytic hypotension. Electrocardiographic, isotopic and echocardiographic investigations have confirmed that periods of subclinical myocardial ischaemia and myocardial stunning occur during haemodialysis (Selby & McIntyre, 2007). Large fluid and electrolyte shifts, low dialysis dose and low pre-dialysis potassium levels are contributing factors (Bleyer et al., 2006; Karnik et al., 2001; Port et al., 2002 Pun et al., 2011). Rates of SCD per dialysis session range from 3.4 in 100.000 to 7.0 in 100.000 dialysis sessions in the outpatient setting and to 12.5 in 100.000 dialysis sessions in hospital-based haemodialysis units (Bleyer et al., 2006; Lafrance et al., 2006). Cardiac arrests are more common on the first dialysis day after a 2-day hiatus (Davis et al., 2008). The risk is particularly high during and immediately after haemodialysis rather than pre-dialysis. Concomitant beta-blocker therapy is beneficial. The risk also declines after renal transplantation.

Data on the incidence of SCD in patients treated with peritoneal dialysis is sparse. Wang et al reported a 25% incidence of SCD in 230 peritoneal dialysis patients which is similar to that in haemodialysis patients (Wang et al., 2010). As fewer abrupt electrolyte shifts occur with peritoneal dialysis than with haemodialysis, it supports the hypothesis that SCD in dialysis patients is predominantly caused by abnormalities of the myocardium common in ESRD rather than the type of dialysis.

3. Interventions to reduce the risk of sudden cardiac death

3.1 Medical interventions

There is evidence from observational and interventional studies that beta-blocker therapy improves outcome in dialysis patients, especially after a cardiac arrest (Cice et al., 2003; Foley et al., 2002; Pun et al., 2007). However, despite this benefit, less than 30% of haemodialysis patients are prescribed beta-blocker therapy (Abbott et al., 2004).

The role of statins in preventing SCD in dialysis patients remains uncertain. The 4D study evaluated the effectiveness of atorvastatin in 1255 haemodialysis patients with diabetes mellitus and found no beneficial effect on cardiovascular mortality, non-fatal myocardial infarction and stroke despite a reduction in LDL cholesterol (Wanner et al., 2005). In contrast, a meta-analysis by Strippoli et al demonstrated that statin therapy in CKD patients significantly reduced lipid concentrations and led to a 20% reduction in non-fatal cardiovascular events (Strippoli et al., 2008). There was no benefit on all-cause mortality.

3.2 Role of implantable cardioverter defibrillator for primary prophylaxis

In patients suffering from reduced left ventricular ejection fraction (LVEF), implantable cardioverter defibrillators (ICD) have emerged as the most effective treatment to reduce the risk of SCD. ICD implantation is recommended for the primary prevention of sudden cardiac death in patients with Class II and III congestive heart failure and decreased LVEF. In patients with refractory heart failure, cardiac resynchronization therapy has been shown to improve symptoms, reduce hospitalizations, and reduce mortality. However, patients with advanced CKD were excluded from most ICD trials despite the fact that the prevalence of left ventricular dysfunction in dialysis patients is reported to be in the vicinity of 14% (Mark et al., 2006).

Data from retrospective analyses showed that CKD patients treated with an ICD for primary prophylaxis against SCD had better outcomes compared to CKD patients treated with conventional therapy alone (Hager et al., 2010). However, there is evidence that ICD efficacy is dependent on renal function. 958 patients with left ventricular dysfunction who had undergone ICD placement for primary prevention of SCD were stratified into 5 groups according to their CKD stage. The median survival time for patients with stage I to V was 78, 90, 80, 42 and 21 months, respectively ($p<0.0001$), and the likelihood of death at 1 year was significantly greater for patients with CKD stage IV or V than for those with stage I. Goldenberg et al came to similar conclusions in their retrospective analysis of patients enrolled into the Multicenter Automatic Defibrillator Implantation Trial (Goldenberg et al., 2006). ICD therapy was only associated with a survival benefit in patients with eGFR ≥ 35 ml/min/1.73m^2 but not in patients with eGFR <35ml/min/1.73m^2. Using a decision analysis model of primary prevention ICD implantation, Amin et al showed that ICD implantation in patients with CKD stage V was only favoured in those aged <65 years (Amin et al., 2008).

The benefit of ICD therapy in dialysis patients is questionable. To date, no randomized clinical trials have been performed in this area. Khan et al reported the impact of ICDs on survival in 78 patients with advanced CKD of whom 45 patients were on dialysis (Khan et al., 2010). In the dialysis cohort, ICD therapy did not impact survival whereas in CKD patients not on dialysis, survival was significantly better in patients with an ICD (2-year survival 80% versus 54%; $p=0.027$). This benefit persisted after adjusting for gender, race, eGFR, digoxin use and presence of coronary heart disease, heart failure, or hypertension.

A meta-analysis on the outcome of patients with an ICD included data of 7 studies with a total of 2516 patients and 89 patients receiving dialysis (Sakhuja et al., 2009). Despite an ICD, dialysis patients had a 2.7 fold higher mortality compared to those not on dialysis. The authors came to the conclusion that ICD therapy did not appear to close the mortality gap between dialysis patients and those not receiving dialysis. This lack of benefit from ICDs in patients with advanced CKD may be explained by more advanced coronary artery disease, concomitant left ventricular hypertrophy, higher propensity for electrolyte imbalances and higher infection risk, all leading to increased susceptibility to arrhythmias and refractoriness to treatment (Dasgupta et al., 2007; Wase et al., 2004). Another proposed mechanism for the reduced benefit may be resistance to ICD therapy with declining renal function. Wase et al found that >35% of dialysis patients had elevated defibrillation thresholds compared to <10% among patients without CKD (Wase et al., 2004).

3.3 Role of implantable cardioverter defibrillator for secondary prophylaxis

Despite the lack of benefit of ICDs in primary prevention of SCDs in dialysis patients, there may be a role for ICDs for secondary prevention in survivors of a cardiac arrest. Retrospective data showed that in patients who survived for 30 days after a cardiac arrest, the median survival in the ICD group was 26 months compared to 11 months in the non-ICD group (Herzog et al., 2005). However, only 8% of the dialysis patients who survived a cardiac arrest episode in fact underwent implantation of an ICD. Patients with an unfavorable clinical status post arrest were excluded.

Considering the high incidence of cardiac deaths in dialysis patients and the cost-effectiveness of ICDs seen in patients with normal or mildly impaired renal function, there is a need for further clinical trials in patients with advanced CKD. Three critical issues

remain: whether there is a role for ICDs in dialysis patients, how to identify those patients who would benefit most from such therapies, and how to achieve even greater prevention, especially primary prevention. Results from "The Implantable Cardioverter Defibrillator in Dialysis patients (ICD2) study" are awaited (De Bie et al., 2008). This prospective randomised controlled study is the first trial which evaluates the possible benefit of prophylactic ICD therapy for the primary prevention of sudden cardiac death in dialysis patients aged 55-80 years with 4-year follow up data.

4. Conclusions

Advanced CKD is associated with a high risk of SCD. Prophylactic ICD implantation has a beneficial role in patients with eGFR > 35ml/min/m^2 but there is less evidence for its use in dialysis patients. Until the results of future trials are available, clinical management needs to focus on preventive strategies, including regular review of the dialysis prescription, avoidance of rapid electrolyte shifts and frequent evaluation of concomitant medication, especially cardioprotective drugs.

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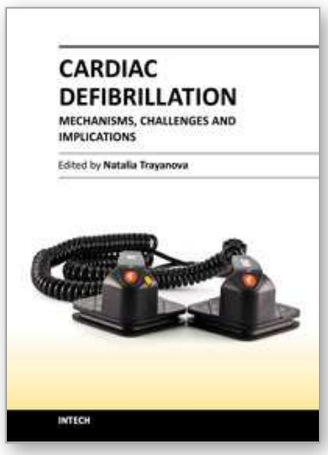

Cardiac Defibrillation - Mechanisms, Challenges and Implications

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The only known effective therapy for lethal disturbances in cardiac rhythm is deï¬brillation, the delivery of a strong electric shock to the heart. This technique constitutes the most important means for prevention of sudden cardiac death. The efficacy of defibrillation has led to an exponential growth in the number of patients receiving implantable devices. The objective of this book is to present contemporary views on the basic mechanisms by which the heart responds to an electric shock, as well as on the challenges and implications of clinical defibrillation. Basic science chapters elucidate questions such as lead configurations and the reasons by which a defibrillation shock fails. Chapters devoted to the challenges in the clinical procedure of defibrillation address issues related to inappropriate and unnecessary shocks, complications associated with the implantation of cardioverter/defibrillator devices, and the application of the therapy in pediatric patients and young adults. The book also examines the implications of defibrillation therapy, such as patient risk stratification, cardiac rehabilitation, and remote monitoring of patient with implantable devices.

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