Editorial

Does the Arrhythmic Risk of Patients with Ischaemic Cardiomyopathy Really Benefit from Revascularisation Therapy?

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One of the most intractable health problems throughout the developed world continues to be sudden cardiac death (SCD). In the USA around 400,000 people per year die from SCD, making up about 63% of all deaths from cardiovascular causes.[1] SCD usually develops on a substrate of ventricular tachycardia or fibrillation, and 80% of its victims suffer from coronary artery disease.[1,2] Conversely, a history of myocardial infarction or heart failure implies an increased risk of SCD, usually because of ventricular tachyarrhythmias.[1-3] More specifically, the risk of SCD increases by 4-6 times in patients with myocardial infarction, and by 6-9 times in those with heart failure.[1,2]

Prevention of SCD

Implantable cardioverter-defibrillator (ICD) devices are a major development in our armamentarium for the primary prevention of SCD and have contributed significantly to a reduction in the mortality of high risk patients, including post-infarction patients with left ventricular dysfunction and patients with heart failure (Figure 1).[1,4-10] There is evidence from large randomised studies to show that ICDs have reduced the incidence of SCD and improved the prognosis of selected high risk patients by terminating life-threatening ventricular tachyarrhythmias.[4-10]

Possible mechanisms of SCD in ischaemic cardiomyopathy

The identification of the mechanisms and presentation of SCD in patients with ischaemic cardiomyopathy is complicated by the fact that such patients comprise a mixed population. These mechanisms have been found to differ depending on the phase of the disease and the time that has elapsed since the initial event.[11] During the early and delayed peri-infarction period, which extends up to 72 hours from the onset of symptoms, sudden death is typically the result of ischaemia that provokes lethal ventricular arrhythmias. Re-entry is one of the main sources of ventricular arrhythmias, but abnormal automaticity and triggered activity also operate. In addition, during the chronic healing phase of an acute myocardial infarction, ventricular arrhythmias occur in patients who suffer from large, often complicated infarcts with severe left ventricular dysfunction. These arrhythmias are the result of local re-entry circuits that include areas of diseased myocardium and electrically unexcitable scars.

New ischaemic events can be superimposed upon this substrate, becoming triggers that provoke a fatal arrhythmia or worsen myocardial failure. Thus, more aggressive anti-ischaemic therapy and revascularisation may be part of the antiarrhythmic regimen in a setting where other

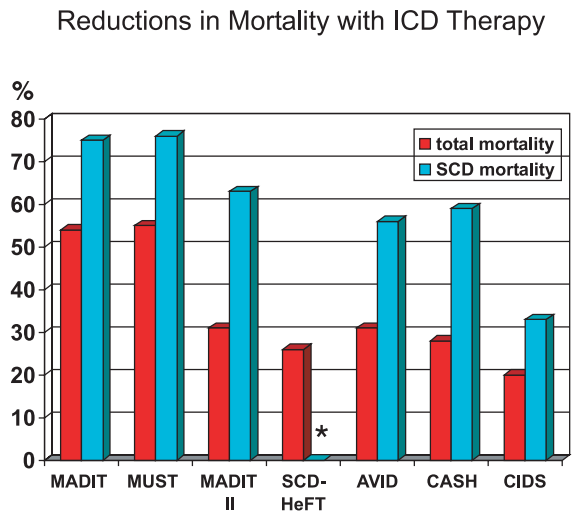

Figure 1. The reduction in mortality associated with ICD implantation in primary prevention trials was equal to or greater than that found in secondary prevention trials. *No data available.

therapeutic modalities are typically stressed. Since myocardial ischaemia appears to be an important trigger for the development of ventricular tachyarrhythmias, the potential influence of revascularisation on the subsequent risk of sudden death is of considerable interest.

Effects of revascularisation on survival

Although there are no completed randomised trials of revascularisation in patients with ischaemic cardiomyopathy, most observational studies have found that revascularisation of hibernating myocardium in this setting improves both survival and left ventricular function compared to drug therapy. The survival benefits are greatest for those patients with the most severe left ventricular systolic dysfunction, the most extensive coronary artery disease, and the most severe anginal symptoms.

Indeed, initial large observational studies, such as the coronary artery surgery study (CASS) and Veterans Administration (VA) cooperative studies, concluded that surgically treated patients experienced a substantial independent reduction in mortality compared with medically treated patients, and that the sicker the patient the greater the benefit—although those studies did not evaluate myocardial viability.[12,13] Subsequent observational studies demonstrated a strong association between survival benefit and revascularisation in patients with chronic coronary artery disease and left ventricular dysfunction who had viable myocardium.[14,15] Absence of myocardial viability on non-invasive testing was not associated with any significant difference in outcomes, irrespectively of treatment strategy.[14,15]

Recently, Veenhuyzen et al evaluated the association between prior revascularisation and future risk of sudden death in a large cohort of patients with ischaemic left ventricular dysfunction. They assessed the effect of prior coronary artery bypass grafting on sudden death in terms of relative and absolute benefit stratified by degree of left ventricular dysfunction.[16] Revascularisation was associated with a significant reduction in the incidence of death from any cause. This reduction was directly attributable to a lower incidence of sudden death, since the largest proportion of deaths was categorised as arrhythmic without preceding heart failure. Therefore, revascularisation reduces both total and arrhythmic mortality.

The improvement in survival after revascularisation in patients with myocardial viability is typically associated with an increase in left ventricular ejection fraction, which is the result of recovery of contractile function after restoration of normal flow to areas of hibernating myocardium.[14,15,17] The reverse ventricular remodelling, which is characterised by reductions in the left ventricular dimensions and volumes, and major alterations in left ventricular shape, also contributes to the improvement of left ventricular function.[14,15,17]

Potential beneficial effects of revascularisation

The genesis of life-threatening ventricular arrhythmias after an acute myocardial infarction is based on complex interactions between an arrhythmic substrate in the form of a damaged myocardium, arrhythmia triggers, and modulating factors such as ischaemia, electrolyte imbalance, autonomic nervous system dysfunction, elevated levels of circulating catecholamines, and toxic cardiac factors, which may act on both substrate and triggers to induce arrhythmias.

In ischaemic cardiomyopathy revascularisation could restore normal flow to areas of hibernating myocardium, minimising adverse ventricular remodelling in remote regions, improving the function of viable dysfunctional myocardial segments, and relieving ischaemia. Reducing the ischaemic burden could decrease the arrhythmic potential and prevent sudden death.

However, it has been established that, by terminating life-threatening ventricular tachyarrhythmias, ICD therapy after a myocardial infarction in patients with left ventricular dysfunction results in significant reduc-

tions in overall and sudden-death mortality compared with antiarrhythmic medication or conventional therapy.[3,6,10] Indeed, the reduction in mortality associated with ICD implantation in primary prevention trials was equal to or greater than that found in secondary prevention trials (Figure1).[3-10] Interestingly, ICDs reduced mortality by 30% to 55% in primary prevention trials, even though the majority of the patients enrolled suffered from coronary artery disease and had undergone revascularisation prior to the ICD implantation (Table 1).[3,6,10]

Does coronary artery revascularisation modify the electrophysiological substrate?

Although coronary artery revascularisation is an effective treatment for myocardial ischaemia, which has been believed to be an important trigger for the development of ventricular tachyarrhythmias, its effect on sudden death that is unrelated to an acute ischaemic event has not been elucidated.

In a recently published study, Brugada et al evaluated both the influence of ischaemia on the occurrence of ventricular arrhythmias, and the effects of coronary artery revascularisation on the inducibility of ventricular arrhythmias, as well as on arrhythmia recurrence during the follow-up period.[18] The authors found that, despite revascularisation, both the inducibility and the recurrence rate of ventricular arrhythmias remained high during follow up. This was attributed to the lack of any significant modification of the arrhythmia substrate.

On the other hand, there is the CABG (coronary artery bypass graft)-patch trial, which included 900 patients who were scheduled for coronary artery bypass surgery, and who had a low ejection fraction and a positive signal-averaged electrocardiogram. The patients were randomised to either ICD implantation or no antiarrhythmic therapy.[19] There was no significant difference in mortality after a mean follow up of 32 months. Interestingly, although ICD therapy reduced arrhythmic death at 42 months by 45 percent (4 versus 6.9 percent in the control group) this reduction did not have an appreciable effect on total mortality, since the vast majority of deaths in this trial were non-arrhythmic.[19]

Similarly, in the MADIT II trial no survival benefit from ICD therapy was seen among patients in whom the device was implanted during the early post-revascularisation period, whereas there was a significant reduction in the risk of all-cause mortality in patients who had undergone revascularisation more than six months before enrolment. In addition, although defibrillator therapy was associated with an overall significant 63% reduction in SCD mortality, this benefit was exclusively attributed to the consistent reduction in the risk of SCD after the early post-revascularisation period.[20] Therefore, in patients with ischaemic cardiomyopathy the benefit from the prophylactic implantation of an ICD after revascularisation seems to be time dependent. According to the results of the MADIT II trial, more than six months after revascularisation there was an increased risk of cardiac death which was the result of a six-fold increase in the risk of SCD.[20]

The time-dependent ICD efficacy in this MADIT II substudy, and the lack of a survival benefit from ICD therapy in the CABG-patch trial, could be attributed to the coronary revascularisation itself, which has such a beneficial effect on the prevention of sudden death.[19,20] Indeed, the distinctive characteristic shared by patients enrolled early and those enrolled late after revascularisation in MADIT II seems to be the probability of recurrent ischaemia.[20] In other words, the lack of a survival benefit from ICD therapy in the aforementioned trials might therefore be attributed to the prevention of recurrent silent or overt ischaemia by revascularisation.

Table 1. The majority of patients in the large ICD trials had coronary artery disease and previous revascularisation.

	MADIT (n=196)	MUSTT (n=704)	MADIT II (n=1232)
Age (years)	63	68	65
Men (%)	92	85	85
LVEF	0.26	0.30	0.23
NYHA II/III (%)	65	64	65
CAD (%)	100	100	100
Previous CABG/PTCA (%)	71	67	57/44
Post-MI (months)	27	39	>36

CABG – coronary artery bypass graft; CAD – coronary artery disease: LVEF - left ventricular ejection fraction; NYHA – New York Heart Association; Post-MI – mean time from myocardial infarction to enrolment. PTCA – percutaneous transluminal coronary angioplasty.

Clinical implications

SCD continues to be one of the most important and intractable health problems, despite the progress that has been made in understanding its pathophysiological mechanisms and the improvements and developments in methods for its management. SCD has a particularly high incidence among patients with myo-

cardial infarction and/or heart failure. Indeed, more than 80% of patients receiving ICDs have a previous myocardial infarction, while nearly all patients who have coronary artery disease undergo coronary revascularisation before ICD implantation. Furthermore, a high percentage of these patients receive ICD shocks despite revascularisation, while ICDs reduced all-cause mortality by almost 40% compared to controls in randomised clinical trials. Thus the risk of sudden cardiac death and arrhythmias remains high in spite of revascularisation, and these patients receive significant benefits from ICDs. However, ICD implantation could be deferred for up to six months after revascularisation, allowing the identification of a potential significant improvement in ventricular function as a consequence of recovery of hibernating myocardium.

In any case we should always keep in mind that revascularisation in ischaemic cardiomyopathy may mainly affect the triggers of arrhythmias, while having a less significant effect on the substrate.

Conclusion

A thorough review of the current literature has taught us that patients with ischaemic cardiomyopathy have a survival benefit if treated by surgical revascularisation. However, the risk of lethal ventricular arrhythmias remains high, particularly in patients with poor left ventricular function. We can therefore conclude that ICD implantation and revascularisation should be complementary forms of therapy.

References

1. Kallergis EM, Vardas PE. Primary prevention of sudden cardiac death: apart from the defibrillator, what is important in patients with myocardial infarction or heart failure? Hellenic J Cardiol. 2007; 48: 89-93.
2. American Heart Association. Heart Disease and Stroke Statistics - 2007 Update. Dallas, Texas: American Heart Association; 2007.
3. Huikuri H, Castellanos A, Myerburg P. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001; 345: 1473-1482.
4. Moss AJ, Hall WJ, Cannom DS, et al; Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med. 1996; 335: 1933-1940.
5. Buxton AE, Lee KL, Fisher JD, et al; Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med. 1999; 341: 1882-1890.
6. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction, reduced ejection fraction. N Engl J Med. 2002; 346: 877-883.
7. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005; 352: 225-237.
8. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997; 337: 1576-1583.
9. Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000; 102: 748-754.
10. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS). A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000; 101: 1297-1302.
11. Bunch TJ, Hohnloser SH, Gersh BJ. Mechanisms of sudden cardiac death in myocardial infarction survivors: insights from the randomized trials of implantable cardioverter-defibrillators. Circulation. 2007; 115: 2451-2457.
12. Alderman EL, Bourassa MG, Cohen LS, et al. Ten year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation. 1990; 82: 1629-1646.
13. The VA Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs Cooperative Study of coronary artery bypass surgery for stable angina. Circulation. 1992; 86: 121-130.
14. Chareonthaitawee P, Gersh BJ, Araoz PA, et al. Revascularization in severe left ventricular dysfunction: the role of viability testing. J Am Coll Cardiol. 2005; 46: 567-574.
15. Tarakji KG, Brunken R, McCarthy PM, et al. Myocardial viability testing and the effect of early intervention in patients with advanced left ventricular systolic dysfunction. Circulation. 2006; 113: 230-237.
16. Veenhuyzen GD, Singh SN, McAreavey D, et al. Prior coronary artery bypass surgery and risk of death among patients with ischemic left ventricular dysfunction. Circulation. 2001; 104: 1489-1493.
17. Carluccio E, Biagioli P, Alunni G, et al. Patients with hibernating myocardium show altered left ventricular volumes and shape, which revert after revascularization: evidence that dyssynergy might directly induce cardiac remodeling. J Am Coll Cardiol. 2006; 47: 969-977.
18. Brugada J, Aguinaga L, Mont L, et al. Coronary artery revascularization in patients with sustained ventricular arrhythmias in the chronic phase of a myocardial infarction: effects on the electrophysiologic substrate and outcome. J Am Coll Cardiol. 2001; 37: 529-533.
19. Bigger JT, Whang W, Rottman JN, et al. Mechanisms of death in the CABG Patch trial: a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. Circulation. 1999; 99: 1416-1421.
20. Goldenberg I, Moss A, McNitt S, et al; for the MADIT-II Investigators. Time dependence of defibrillator benefit after coronary revascularization in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. J Am Coll Cardiol. 2006; 47: 1811-1817.