Non-arrhythmic therapy of ventricular tachyarrhythmias and sudden cardiac death after acute myocardial infarction

P. Schweitzer

Division of Cardiology, Department of Medicine, Beth Israel Medical Center and Albert Einstein College of Medicine, New York, USA

Prednesené na vedeckej pracovnej schôdzi Spolku lekárov v Košiciach dňa 25. apríla 2006 na XIII. memoriáli profesora F. Póra.

Summary: The management of ventricular tachyarrhythmias and prevention of sudden cardiac death after acute myocardial infarction (AMI) underwent important evolution. In the CAST study, encanaide and other antiarrhythmic drugs were not only ineffective but also increased mortality after myocardial infarction. Amiodarone had some beneficial effect on arrhythmic events without improving survival, and ICDs failed to improve outcome early after AMI. In comparison, short and long term survival benefits of beta blockers, angiotensine converting enzyme inhibitors and aldosterone antagonists after AMI is well established. This review discusses the role of non-arrhythmic therapy in the prevention of ventricular tachyarrhythmia's and sudden cardiac death after AMI.

Key words: ventricular tachyarrhythmias – sudden cardiac death – acute myocardial infarction

Nearytmická terapie komorových tachyarytmií a náhlá srdeční smrt po akutním infarktu myokardu

Souhrn: Ve vývoji managementu komorových tachyarytmií a prevenci náhlé srdeční smrti po akutním infarktu myokardu (AIM) došlo k významu posunu. Encainid a další antiarytmické léky použité v studii CAST byly nejenom neúčinné, ale zvyšovaly mortalitu po infarktu myokardu. Amiodaron měl některé pozitivní účinky na arytmické příhody, aniž by zvyšoval míru přežívání, a přínos ICD ke zlepšení výsledků krátce po AIM se neprokázal. Na druhé straně přínos beta-blokátorů, angiotenzin konvertujících inhibitorů a antagonistů aldosteronu z hlediska krátkodobého a dlouhodobého přežívání po AIM je prokázán. Referát pojednává o roli nearytmické terapie v prevenci komorové tachyarytmie a náhlé srdeční smrti po AIM.

Klíčová slova: komorová tachyarytmie – náhlá srdeční smrt – akutní infarkt myokardu

The management of ventricular tachyarrhythmias after acute myocardial infarction (AMI) remains an important clinical problem. One of the first randomized studies (CAST) with encanaide and flecainide [1] not only failed to improve survival after AMI but also increased its mortality. These results were followed by two studies with amiodarone (EMIAT and CAMIAT) [2,3], both showing beneficial effect on arrhythmic events without improving total and cardiovascular mortality. The beneficial effect of ICDs in patients after myocardial infarction and left ventricular dysfunction was confirmed in several studies [4,5]. However, as shown by Hohnloser et al [6], ICD therapy failed to improve survival early after AMI [6] when the incidence of SCD is the highest [7]. In comparison, revascularization [8–10], beta blockers [11–14], angiotensine converting enzyme inhibitors (ACEI) [15], and aldosterone antagonist [16] all improved outcome after AMI. The purpose of this review is to discuss the role of these therapies in the prevention of sudden cardiac death (SCD) and ventricular tachyarrhythmias early post-AMI.

Among important risk factors post-AMI are age and left ventricular dysfunction, with or without heart failure. Elderly patients have higher total and cardiovascular mortality after AMI, while the incidence of SCD moves in opposite direction.

Abildstrom et al [17] using the data from the TRACE study, compared the incidence of SCD and non–SCD in patients at different age group and found that the ratio of SCD to non-SCD gradually decreased with age. The incidence of SCD in patients over 75 years of age was 40 % of those 55 years of age or younger. Another important risk factor after AMI is left ventricular function and congestive heart failure. According to the second national registry of myocardial infarction [18], in-hospital mortality was higher in patients in Killip's class II or III than in class I. In addition, these patients were older, had higher incidence of anterior myocardial infarction and were less likely managed with beta-blockers or revascularization. Similarly, in the GRACE study [18], the mortality after AMI was almost 3 times higher in patients presenting with heart failure on admission. Other risk factors for SCD and cardiovascular mortality are post-infarction myocardial ischemia, ventricular tachyarrhythmias, re-infarction, diabetes mellitus and renal insufficiency [20].

The role of beta blockers in prevention of SCD

Beta blockers were the first drugs showing survival benefit after AMI [11,12]. The majority of early studies were done before thrombolysis or other forms of revascularization mostly in patients with preserve left ventricular function. In general tomfool, metoprolol and propranolol reduced the incidence of SCD between 21–51 % [11,12]. Chadda et al [21] first reported beneficial effect of propranolol in patients with history of heart failure.

The two recent reports dealing with this subject were the COMMITT [13] and CAPRICORN [14] studies. In the first one, metoprolol was administered intravenously followed by oral therapy for one month in 45,852 patients with suspected AMI. Thrombolysis, ACEI and different antiarrhythmic drugs were used in 54 %, 67 % and 22 % of patients respectively. Metoprolol prevented ventricular fibrillation and re-infarction, while increased the incidence of cardiogenic shock. The end result of the COMMITT study was no survival benefit of metoprolol, because prevention of ventricular fibrillation was outweigh by higher incidence of cardiogenic shock. The second randomized study [14] evaluated the effect carvedilol after AMI and impaired left ventricular function. This study included almost 2000 post-AMI patients with left ventricular ejection fraction < 40 %. Randomization started between 3–21 days after AMI and background therapy included 97 and 98 % ACEI, 86 % aspirin and 45 % of patients underwent thrombolysis. Amiodarone and other antiarrhythmic drugs were used in 5 % of patients. The original endpoint was all-cause mortality which was extended to hospitalization of cardiovascular causes, SCD, and non-fatal myocardial infarction. The main results of the CAPRICORN study were significant decrease of total and cardiovascular mortality and non-fatal myocardial infarction.

In a follow up study, McMurray et al [22] reported the effect of carvedilol on the incidence of atrial and ventricular tachyarrhythmias, confirming its beneficial effect on all types of ventricular arrhythmias including the so called „malignant ones“ without preventing SCD. The relatively small number of patients dying suddenly and some non-arrhythmic causes of SCD could explain this finding [22].

The beneficial effect of beta blockers after AMI is also supported by additional observations. Gottlieb et al [23] reviewing the Cooperative Cardiovascular Project study, reported 40 % lower mortality of patients taking beta blockers. In addition, this study of 201,752 patients, showed that beta blockers were less frequently used in patients with impaired left ventricular fraction, diabetes mellitus, elderly and non–ST segment elevation myocardial infarction. The potentiation of the beneficial effect of ACEI with beta blockers was demonstrated by Spargias et al [24] in the AIRE sub-study. Adding beta blockers to Ramipril further improved survival of patients after AMI, prevented the development of heart failure and decreased the use of diuretics. Beta blockers also had beneficial effect on the outcome after percutaneous revascularization [25,26] and decreased the mortality in patients after myocardial infarction with impaired left ventricular function and non–sustained ventricular tachycardia [27]. In the MADIT II study, beta blockade decreased the incidence of appropriate shock and reduced mortality [28].

As reviewed, in addition to the beneficial effect of beta blockers on total and cardiovascular mortality these agents could also prevent SCD, particular with timolol, propranolol and metoprolol [11,12,21]. However, in more recent studies, metoprolol and carvedilol failed to decrease the incidence of SCD [13,14]. Among the possible explanations for this finding are the following. First, the number of patients in the CAPRICORN study was too small to show significant effect of carvedilol on SCD [22]. Second, more patients were revascularized and treated with ACEI both of which are known to lower the risk of SCD. Third, in the COMMIT study higher incidence of cardiogenic shock outweigh the beneficial effect of metoprolol on SCD [13].

The role of angiotensine-converting enzyme inhibitors on SCD

The beneficial effect of ACEI on outcome of patients after AMI, particularly those with impaired left ventricular function is well established

[29–33]. The SAVE study [29] was one of the first, demonstrating survival benefit of captopril in patients after myocardial infarction and left ventricular dysfunction. Subsequent studies confirmed these results on total and cardiovascular mortality [30–33] and some but not all also showed lower incidence of SCD [30,31].

ACEI could prevent SCD by the following mechanisms. In addition to stabilization of the arteriosclerotic lesions and their effect on smooth muscle, ACEI inactivate platelets, increase nitric oxide production and block the sympathetic nervous system. ACEI further prevent ventricular hypertrophy and fibrosis which are important structural abnormalities in the pathogenesis of tachyarrhythmias.

There are two studies showing, beneficial effect of ACEI on SCD [30,31]. In the TRACE study [30] 1,749 patients were dividend into two groups receiving either oral trandolapril or placebo. Trandolapril, in addition to significant survival benefit, also lowered the incidence of SCD by 25 %. In the second study (AIRE) [31] ramipril was compared with placebo in 2,006 patients with heart failure. The primary endpoint was total mortality. In a follow up report, ramipril decreased the incidence of SCD by 30 % [34]. The TRACE and AIRE studies were followed by a meta–analysis of 15 studies [15], which included patients within 14 days after AMI and ACEI therapy for more than 6 weeks. In studies with 500 patients or more there was either a significant or a trend in the reduction of SCD risk [15].

The survival benefit of ACEI in patients after AMI ranges between 16 to 26 %. One possible explanation for this modest effect of ACEI in AMI could be an incomplete blockade of angiotensine II. This assumption was tested in subsequent studies [35,36] using angiotensine receptor blockade alone or in combination with ACEI. Dickstein et al [35] compared losartan with captopril, showing slightly better results with the latter. In a much larger study of VALIANT, Pfeffer et al [36] compared valsartan with captopril. An unexpected finding of the VALIANT study was similar efficacy of valsartan and captopril or their combination on total and cardiovascular mortality. In the VALIANT study, SCD was not an endpoint.

The role of aldosterone blockade in SCD after AMI

Aldosterone has multiple adverse cardiovascular effects some of which could play a role in the pathogenesis of ventricular tachyarrhythmias after AMI [37]. First, aldosterone contributes to left ventricular remodeling which includes left ventricular architectural changes, expansion and tinning of the necrotic area and, enlargement of the left ventricular cavity. Left ventricular remodeling is an important cause of left ventricular dysfunction. Second, aldosterone causes endothelial dysfunction, vasoconstriction and platelet activation. Third, aldosterone increases sympathetic tone, myocardial fibrosis and ventricular hypertrophy. In other words, all these structural and functional changes of aldosterone could contribute to its arrhythmogenic effects.

In 2003 Pitt et al [16] reported the effects of eplerenone, a new aldosterone antagonist, in patients after AMI. This study randomized 6,632 patients after AMI with heart failure or low left ventricular ejection fraction (< 40 %) to eplerenone or placebo. Background therapy included ACEI in 87 %, beta-blockers in 75 %, statins in 47 %, diuretics in 60 % and aspirin in 88 % of patients. Eplerenone reduced the relative risk for all causes and cardiovascular mortality by15 % and 17 % respectively with similar effect on hospitalization for heart failure The main adverse effects of eplerenone were 5.5 % hyperkalemia and gynecomastia. Impotence, breast pain and menstrual irregularities, were similar in both groups.

In a subsequent study, Pitt et al [38] showed that in the first month after randomization, eplerenone lowered the relative risk of SCD by 58 %. This observation is important and justifies early therapy with eplerenone in patients with impaired left ventricular function and or congestive heart failure after AMI. The mechanism of the early protective effect of eplerenone is not completely clear. Some experimental studies suggest that aldosterone blockade [39], normalizes calcium and potassium current and shortens the action potential duration after AMI. These electrophysiological changes, which occur before structural remodeling, might prevent life threatening tachyarrhythmias.

Conclusions

Beta-blockers, ACEI and aldosterone antagonists play an important role in the management of patients after AMI. In addition to their beneficial effect on total and cardiovascular mortality, these drugs could also prevent SCD. Because the highest incidence of SCD is in the first month after AMI, these drugs should be used as early as possible. Another important intervention in patients after AMI with left ventricular dysfunction, not discussed in this review, is myocardial revascularization.

References

1. The cardiac Arrhythmias Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321: 406–412.
2. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 349: 667–674.

3. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarization: CAMIAT. Lancet 1997; 349: 675–682.
4. Moss AJ, Hall WJ, Cannon DS et al. Improved Survival with an implantable defibrillator in patients with coronary artery disease at high risk for ventricular arrhythmias. N Engl J Med 1996; 335: 1933–1940.
5. Moss AJ, Zareba W, Hall WJ et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877–883.
6. Hohnloser SH, Kuck KH, Dorian P et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004; 351: 2481–2488.
7. Solomon SD, Zelenkofske S, McMurray JJV et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure or both. N Engl J Med 2005; 352: 2581–2588.
8. Holmes DR Jr, Davis KB, Mock MB et al. The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the coronary artery surgery study. Circulation 1986; 73: 1254–1263.
9. Bigger JT for the coronary artery bypass graft (CABG) patch trial investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass graft surgery. N Engl J Med 1997; 337: 1569–1575.
10. Makikallio TH, Barthel P, Schneider R et al. Frequency of sudden cardiac death among acute myocardial survivors with optimized medical and revascularization therapy. Am J Cardiol 2006; 97: 480–484.
11. Olsson G, Wikstrand J, Warnold I et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. Eur Heart J 1992; 13: 28–32.
12. Hjalmarson A. Effect of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. Am J Cardiol 1997; 80: 35J–39J.
13. COMMIT (Clopidrol and Metoprolol in myocardial infarction trial) collaborative group. Early intravenous then oral metoprolol in 45852 patients with acute myocardial infarction randomized placebo-controlled trial. Lancet 2005; 366; 1622–1632.
14. The CAPRICORN Investigators. Effects of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomized trial. Lancet 2001; 357: 1385–1390.
15. Domanski MJ, Exner DV, Borkowf CB et al. Effect of angiotensine converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. J Am Coll Cardiol 1999; 33: 598–604.
16. Pitt B, Remme W, Zannad F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348: 1309–1321.
17. Abildstrom AZ, Rask–Madsen C, Ottsen MM et al on behalf of the TRACE study group. Impact of age and sex on sudden cardiovascular death following myocardial infarction. Heart 2002; 88: 573–578.
18. Wu AH, Parsons L, Every NR et al. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction. J Am Coll Cardiol 2002; 40: 1389–1394.
19. Steg PG, Dabbous OH, Feldman LJ et al. Determinants and prognostic impact of heart failure complicating acute coronary syndrome; Observation from the global registry of acute coronary events (GRACE). Circulation 2004; 109: 494–499.
20. Yap YG, Duong T, Bland M et al. Temporal trend on the risk of arrhythmic vs. nonarhhytmic high–risk patients after myocardial infarction: a combined analysis of multicenter trial. Eur Heart J 2005; 26: 1385–1393.
21. Chadda K, Goldstein S, Byington R et al. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986; 73: 503–510.
22. McMurray J, Kober L, Robertson M et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction; Results of the carvedilol post-infarct survival control in left ventricular dysfunction (CAPRICORN) trial. J Am Coll Cardiol 2005; 45: 525–530.
23. Gottlieb SS, Carter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low risk patients after myocardial infarction. N Engl J Med 1998; 339: 489–497.
24. Spargias KS, Hall AS, Greenwood DC et al. Beta blocker treatment and other prognostic variables in patients with clinical evidence of heart failure after acute myocardial infarction: evidence from the AIRE study. Heart 1999; 81: 25–32.
25. Ellis K, Tcheng JE, Sapp S et al. Mortality benefit of beta blockade in patients with acute coronary syndrome undergoing coronary intervention: Pooled results from epic, epilog, capture and rapport trial. J Interven Cardiol 2003; 16: 299–305.
26. Kernis SJ, Harjai KJ, Stone GW et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? J Am Coll Cardiol 2004; 43: 1773–1779.
27. Ellison KE, Hafley GE, Hickey K et al. Effect of beta-blocking therapy on outcome in the multicenter unsustained tachycardia trial (MUSTT). Circulation 2002; 106: 2694–2699.
28. Brodine WN, Tung RT, Lee JK et al. Effects of beta-blockers on implantable cardioverter defibrillator therapy and survival in patients with ischemic cardiomyopathy (from the multicenter automatic defibrillator implantation trial-II). Am J Cardiol 2005; 96: 691–695.
29. Pfeffer MA, Braunwald E, Moye LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and ventricular Enlargement Trial. N Engl J Med 1992; 327: 669–677.
30. Kober L, Torp–Pedersen C, Carlsen JA et al. A clinical trial of the angiotensine-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995; 333: 1670–1676.
31. The acute infarction ramipril efficacy (AIRE) study investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821–828.
32. Ambrosioni E, Borghi C, Magnani B for the survival myocardial infarction long-term evaluation (SMILE) study investigators. N Engl J Med 1995; 332: 80–85.
33. Swedberg K, Held P, Kjekshus J et al. On behalf of the CONSENSUS II study group. N Engl J Med 1992; 327: 678–684.

34. Cleland JGF, Erhardt L, Murray G et al. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: A report from the AIRE study investigators. Eur Heart J 1997; 18: 41–51.
35. Dickstein K, Kjekshus J and the OPTIMAL Steering Committee. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAL randomized trial. Lancet 220; 360: 752–760.
36. Pfeffer MA, McMurray JJ, Veleazguez EJ et al. Valsartan in acute myocardial infarction trial investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003; 349: 1893–1906.
37. John JN, Colucci W. Cardiovascular effects of aldosterone and post–acute myocardial infarction pathophysiology. Am J Cardiol 2006; 97(Suppl): 4F–12F.
38. Pitt B, White H, Nicolau J et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005; 46: 425–431.
39. Perrier E, Kerfant BG, Lalevec N et al. Mineralcorticoid receptor antagonism prevents the electrical remodeling that precedes cellular hypertrophy after myocardial infarction. Circulation 2004; 110: 776–783.

Paul Schweitzer M.D.
Division of Cardiology,
Beth Israel Medical Center
1st Av at 16th Street
New York, N.Y. 10003, USA
e-mail: Pschweit@chpnet.org

Doručeno do redakce: 15. 8. 2006