Arrhythmias in ischemic heart disease

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Correlation between C-reactive protein and ventricular arrhythmias during the acute phase of myocardial infarction

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Background. **Tissue necrosis is a potent acute-phase stimulus. During the acute phase of myocardial infarction (AMI), there is a major C-reactive protein (CRP) response, the magnitude of which probably reflects the extent of myocardial necrosis. The CRP peak values in the post-infarction period strongly predict outcomes after myocardial infarction. The aim of this study was to determine whether elevated plasma concentrations of CRP at the beginning of myocardial infarction were associated with early ventricular arrhythmias.**

Methods. **We studied 27 consecutive patients with AMI (25 males, 2 females, mean age 63.7 ± 11.97 years) admitted to the Intensive Care Unit within 3 hours of symptom onset. In all patients the CRP concentration was evaluated after 6 hours from the time of admission. The presence of ventricular arrhythmias, classified according to Lown classes, was evaluated through a 24-hour Holter monitoring, recorded just after the blood sampling. For statistical evaluation the Student's t-test and analysis of covariance were performed. A p value of < 0.05 was considered as statistically significant.**

Results. **Lown classes 4-5 were associated with higher CRP values (p = 0.002) and lower ejection fraction (p = 0.006). Increased CRP levels remained significantly correlated with poor Lown class even after adjustment for ejection fraction (p = 0.003). At *post-hoc* analysis Lown classes 4-5 showed higher CRP values than Lown class 0 (p = 0.003) and Lown classes 1-3 (p = 0.011).**

Conclusions. **In patients with AMI elevated CRP levels within the sixth hour after admission seem to be an interesting potential risk marker of early ventricular arrhythmias, whose definite relevance remains to be established.**

A growing number of studies report that C-reactive protein (CRP) levels increase after the onset of acute myocardial infarction (AMI)[1,2]. The elevation in CRP levels correlates with in-hospital and short-term adverse prognosis[3,4] independently of the extent of myocardial damage and may reflect a higher prevalence of myocardial necrosis and ischemia-reperfusion damage. However, the correlation between cardiac arrhythmic events and plasma concentrations of CRP during the acute phase of myocardial infarction is unknown. We, therefore, sought to assess whether plasma concentrations of CRP at the beginning of myocardial infarction are predictive of early occurrence of ventricular arrhythmias.

Methods

We studied 27 consecutive patients (25 males, 2 females, mean age 63.7 ± 11.97 years) with AMI admitted to the Intensive Care Unit within the third hour after symptom onset. Blood samples were obtained at the sixth hour after admission. Plasma concentrations of CRP were determined using the particle enhanced turbidimetric immunoassay technique. A 24-hour Holter monitoring was recorded just after blood sampling, using Reynolds Pathfinder digital devices.

Statistical analysis. Results are expressed as mean ± SD for continuous variables. Qualitative data are reported as number. Comparisons have been performed by using independent Student's t-test, analysis of covariance and *post-hoc* Newman-Keuls test ("Statistica 6.0; StatSoft Inc." software). A p value < 0.05 was considered as statistically significant.

Results

The Holter monitoring identified 8 patients belonging to Lown class 0 (mean age

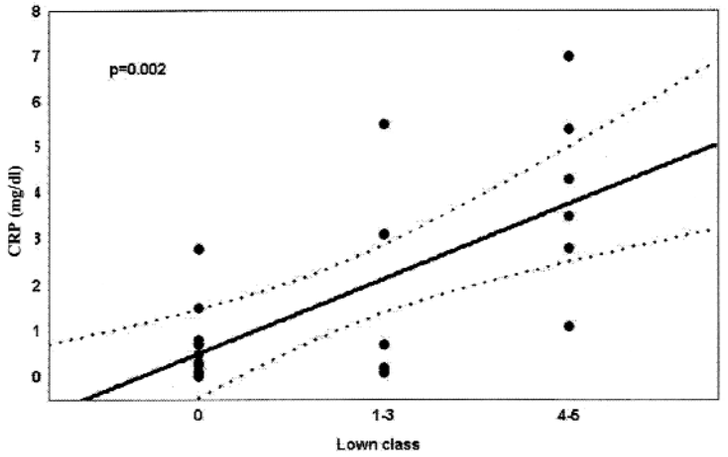

Figure 1. *Correlation between Lown class and C-reactive protein (CRP) levels.*

59.42 ± 14.36 years), 12 patients to Lown classes 1-3 (mean age 70 ± 7.57 years), and 7 patients to Lown classes 4-5 (mean age 63.85 ± 9.29 years). CRP values at the sixth hour after admission were significantly higher in patients belonging to Lown classes 4-5 (3.71 ± 2.04 mg/dl) in comparison to patients belonging to Lown classes 1-3 (1.36 ± 1.93 mg/dl, p = 0.039) and to patients belonging to Lown class 0 (0.6 ± 0.81 mg/dl, p = 0.0002); there were no statistically significant differences between CRP levels in patients with Lown classes 0 and 1-3. The three groups were similar for gender, risk factors, history, and cholesterol plasma level. Lown classes 4-5 were associated with higher CRP levels (p = 0.002) (Fig. 1) and lower ejection fraction (p = 0.006). CRP remained significantly correlated with poor Lown class even after adjustment for ejection fraction (p = 0.003). At *post-hoc* analysis Lown classes 4-5 showed higher CRP values than Lown class 0 (p = 0.003) and Lown classes 1-3 (p = 0.011). There were no significant differences between Lown classes 0-3 (p = 0.26). CRP and ejection fraction were significantly correlated (r = -0.45, p = 0.03).

Discussion

Many studies have shown that plasma levels of CRP are associated with the presence and the severity of coronary, cerebral and peripheral artery disease[5-8]. Furthermore, increased plasma concentrations of CRP also increase the risk of short-term cardiovascular outcomes[9-11]. Very few studies have addressed the relation between CRP and in-hospital risk of ventricular arrhythmias. Previous investigations[7] demonstrated the connection between CRP release and myocardial damage through the local activation of the complement system. Our results suggest that the severity of ventricular arrhythmias is related to CRP levels during the first phase of AMI. The significance of this correlation could be explained by the increased production of CRP that predicts cardiac events which may reflect a previous inflammation due to microbial agents, such as *Chlamydia pneumoniae*, that have been linked to coronary artery disease.

The inverse correlation between ejection fraction and CRP levels suggests a possible link between extension of myocardial damage, CRP levels and ventricular arrhythmias. Whether myocardial damage acts on ventricular instability through CRP release or myocardial damage, or if CRP release and ventricular arrhythmias are related in some other ways, remains to be defined. The link between plasma CRP concentrations and the Lown classes expresses the relevance of the inflammatory cytokine network activation in the electric instability during the acute phase of a coronary syndrome.

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INCIDENCE OF ARRHYTHMIAS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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The profile and management of arrhythmias during the last 30 years has changed. In the era of thrombolysis and coronary angioplasty the incidence of arrhythmias decreases. In the early days of coronary care units extrasystoles were treated under the aspect to prevent malignant arrhythmias. Now only ventricular tachycardias/fibrillation are an indication for pharmacological or non-pharmacological treatment depending on the hemodynamic state of the patient.

Arrhythmias especially in patients with impaired left ventricular function have prognostic implications. This has to be taken into consideration in the further management of patients at discharge.

Introduction

Since the early '70s patients with acute myocardial infarction (AMI) are treated in coronary care units (CCU). Continuous monitoring was a milestone in the management of arrhythmias. Numerous articles dealing with the incidence, treatment and prognostic significance of arrhythmias have been published. This article gives a survey and includes an overview about the management of patients with AMI in Austria 1990-2001. This survey was organized by the Austrian Heart Foundation and the Ludwig Boltzmann Institute for Arrhythmia Research and collected data of 14 100 patients with AMI.

Supraventricular arrhythmias

Supraventricular extrasystoles occur in patients with AMI with the same incidence rate as in the general population. They have clinical significance as precursor of atrial fibrillation. There are only few reports in the literature concerning the incidence of atrial tachycardia and atrial flutter, they are rare events in this patient group.

Atrial fibrillation in patients with AMI is reported with an incidence between 5 and 20%[1]. In female even age-adjusted the risk is significant higher than in male patients[2]. Patients with atrial fibrillation and hemodynamic complications have a significant higher mortality rate[3].

In the Austrian CCU survey supraventricular arrhythmias ranged between 18 and 32% over a 12-year period (Fig. 1).

Supraventricular arrhythmias in patients with heart failure during the acute phase influence the long-term prognosis[4,5]. The increased risk of mortality mostly is due to their worse risk profile[6,7]. Amiodarone has no influence on mortality[8].

Ventricular arrhythmias

Ventricular extrasystoles occur frequently in patients with AMI[9-11]. They are still classified according to the proposal of Bernard Lown. In the early period of CCU they have been aggressively treated with drugs. The

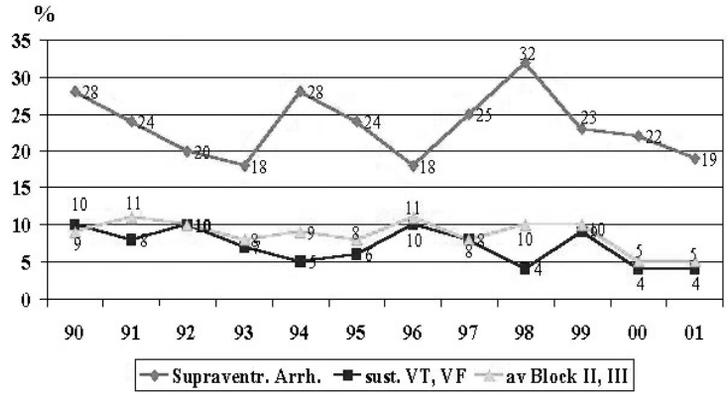

Figure 1. *Arrhythmias. av = atrioventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.*

influence of ventricular extrasystoles class ≥ IV on morbidity and mortality is well established, but the prognosis depends mainly on the degree of impaired left ventricular function[12,13].

About half of patients with AMI have non-sustained ventricular tachycardias defined as ≥ 3 consecutive ventricular complexes. They are imperfect for selection of patients at risk for sustained ventricular tachycardia or fibrillation[11].

Like ventricular extrasystoles they are not an independent risk factor concerning arrhythmogenic events during follow-up[14]. Programmed ventricular stimulation is not able to select patients with a higher risk[15].

Published data of the incidence rates of primary ventricular fibrillation in patients with AMI suggest that the rate ranges between 2 and 8%[16,17]. This is true also for sustained ventricular tachycardia. The incidence reported in the Austrian CCU survey, where sustained ventricular tachycardia and ventricular fibrillation were grouped together dropped from 1990 to 2001 from 10 to 4%[18] (Fig. 1). The decrease could be explained by the improvement of the management of patients with AMI. During this time the percentage of patients treated with thrombolysis increased from 20 to 33% in female and from 34 to 40% in male patients.

Also in patients with sustained ventricular tachycardia and ventricular fibrillation the prognosis depends on the function of the left ventricle[19-21].

Conduction defects

Approximately 6% of patients with AMI, most of them with inferior localization, develop complete atrioventricular block. The block in most instances is transient and ascribed to atrioventricular node ischemia[22]. The Austrian CCU survey reported an incidence scattering between 5 and 11% (Fig. 1).

Bundle branch block, bifascicular block occur mainly in anterior AMI and has a high mortality in most cases because of pumps failure.

Treatment

Beta-blockers are routinely used independently of the rhythm profile of patients, also because of their antiarrhythmic properties[23].

In the Austrian CCU survey from 1990 till 2001 the percentage of patients treated with beta-blockers increased from 30 to 71%[18] (Fig. 2). Only few data concerning other antiarrhythmic drugs are available. In our survey < 5% received class I or class III drugs at discharge (Fig. 3). Extrasystoles *per se* are not an indication for an antiarrhythmic treatment as well during hospital stay as at discharge. Their management should be incorporated into an overall treatment strategy for the patient at risk.

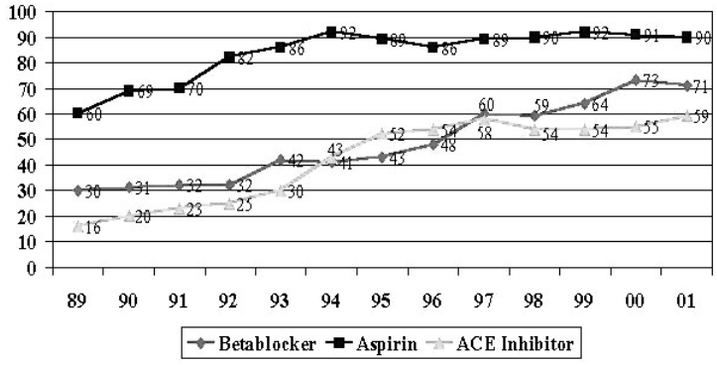

Figure 2. *Treatment at discharge.*

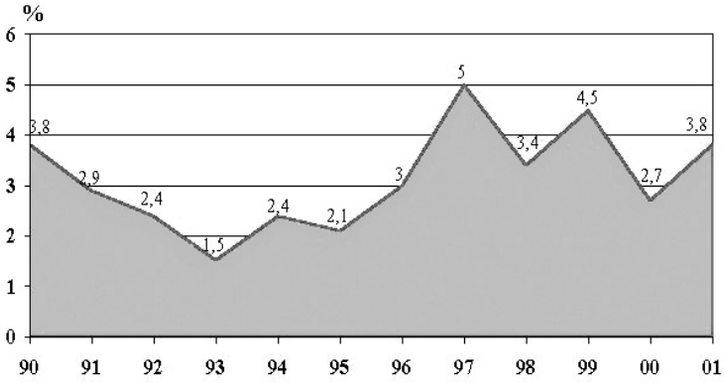

Figure 3. *Antiarrhythmic treatment at discharge.*

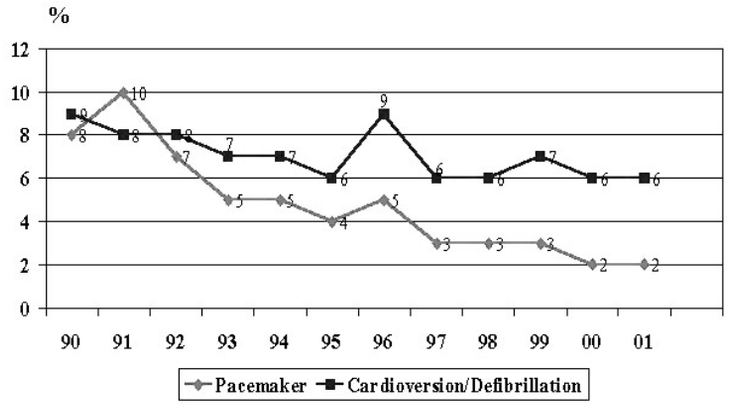

Figure 4. *Interventions in arrhythmias.*

Rate control in atrial fibrillation is adequate, if not hemodynamic complications require immediate cardioversion. The same is true for atrial tachycardia. Pharmacological cardioversion is effective in most patients with atrial flutter.

Immediate cardioversion/defibrillation of ventricular tachycardia and ventricular fibrillation has reduced the mortality in the acute state and is superior to drug treatment[24]. The prophylactic use of antiarrhythmic drugs has dropped dramatically. Even lidocaine in the prehospital phase as in the CCU is not routinely used[11].

Temporary pacing in patients with total atrioventricular block is routinely used. In the Austrian CCU survey the use of temporary pacemaker decreased from 10 to 2% from 1990 to 2001 (Fig. 4). There is no place for drugs. In patients with anterior AMI and atrioventricular block or bundle branch block pacing has not improved the prognosis. Patients die because of pump failure if they are not treated with hemodynamic assist devices and coronary angioplasty or bypass surgery.

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ROLE OF REVASCULARIZATION PROCEDURES IN THE PREVENTION OF SUDDEN CARDIAC DEATH

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Sudden cardiac death often occurs in the setting of coronary artery disease[1]. Furthermore, it has been shown that in patients with coronary artery disease and low left ventricular ejection fraction, as much as 50% of all deaths are sudden[2].

Sustained ventricular arrhythmias are most frequently responsible for this event[3]. This is not surprising since acute myocardial ischemia is an important potential trigger of fatal arrhythmias[4]. As a consequence, myocardial revascularization has been advocated since the early phases of its availability as a means of decreasing sudden death in patients with ischemic heart disease[5].

Moreover as a further support to this strategy, revascularization has been shown to improve electrical stability in patients with coronary heart disease and to result in a lower inducibility rate of serious arrhythmias in some studies[6]. However, in others an inducibility rate of 13% has been demonstrated even after successful revascularization[7,8].

The widespread use of implantable cardioverter-defibrillators (ICD) has changed the scenario but a randomized study, the CABG Patch trial, found a lack of benefit from ICD implantation in patients undergoing surgical revascularization[9].

More recent studies have addressed the issue of prevention of sudden cardiac death by the use of revascularization procedures[10,11]. In a investigation of 5410 patients with coronary artery disease and left ventricular dysfunction from the SOLVD study, Veenhuyzen et al.[10] concluded that in patients with coronary disease and low ejection fraction, coronary artery bypass grafting is associated with a significant independent reduction in mortality.

On the other hand, van der Burg et al.[11] found in 153 survivors of sudden death who underwent assessment by technetium-99-m single photon emission computed tomography, that extensive scar tissue and severely depressed left ventricular ejection fraction are the only predictors of death or recurrent ventricular arrhythmias, therefore suggesting ICD implantation in all such patients. However, in the same study, patients with areas of myocardium jeopardized by ischemia who underwent revascularization had a low event rate (13%) as compared to medically treated patients (38%).

Therefore, revascularization of myocardium at risk should be advised to reduce adverse events.

In conclusion, we believe that revascularization plays a role in the prevention of sudden cardiac death in patients with coronary artery disease, particularly if severe left ventricular dysfunction and myocardial ischemia/viability are present. ICD implantation has to be considered advisable in most cases and particularly so if extensive scar tissue is demonstrated by non-invasive/invasive testing.

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