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Rapid communication

Delay in opening the infarct related coronary artery increases plasma atrial natriuretic peptide levels

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Abstract

Plasma atrial natriuretic peptide (ANP) levels were measured in rabbits during the late healing phase of myocardial infarcts. Significant differences in plasma ANP levels ($P < 0.02$) were found between rabbits that had undergone very late (6 h) or early reperfusion (20 and 45 min of ischemia) of the infarct related coronary artery. Differences in ANP levels were independent of infarct size, ventricular remodeling and infarct expansion. We conclude late reperfusion of infarct related artery, independent of myocardial salvage, is associated with increased circulating ANP plasma levels.

Keywords: ANP (atrial natriuretic peptide); Myocardial infarction; Reperfusion, late

Atrial natriuretic peptide (ANP) is located in granules within atrial myocytes of the normal heart (Levin et al., 1998). In response to pathological atrial stretch, increased levels of ANP are released into the circulation (Levin et al., 1998) and produce a variety of haemodynamic effects, including intrinsic diuretic and natriuretic effector responses in the kidney (Levin et al., 1998). ANP is also expressed in the ventricular myocardium during foetal heart development. Both ANP and its analogue, brain natriuretic peptide (BNP), are expressed in the ventricle in response to pressure overload in adult hypertrophied hearts (Levin et al., 1998). Raised plasma levels of ANP have also been found in patients following an acute myocardial infarct, for at least 30 days post-infarct (Nagaya et al., 1998). The ANP level directly correlates with impaired ventricular function, post-infarct remodeling (chamber dilatation, hypertrophy and wall thinning) and independent predictors of mortality (Hall et al., 1994).

Early reperfusion of the infarct related coronary artery will usually result in the salvage of affected myocardium, while late reperfusion will not. However, both early and late reperfusion are associated with a reduction in mortality and inhibition of infarct expansion and subsequent ventricular remodeling (Solomon and Gersh, 1998).

Nagaya et al. (1998) examined natriuretic peptide plasma levels for 30 days post infarction. Significantly increased levels were observed in the late/no reperfusion patient group, compared to the early, sustained reperfusion patient group. However, these data did not differentiate between the effect of late reperfusion and no reperfusion. The aim of this study was to use a rabbit model of myocardial infarction to determine whether plasma natriuretic peptide levels were elevated following late reperfusion, i.e., during the late infarct healing and the remodeling processes.

These experiments conform to the international guiding principals for the care and use of laboratory animals and the ethics committee of the University of Sydney has approved the experimental protocol applied.

Twenty-eight adult New Zealand White rabbits (2.6–3.5 kg), of either sex, were randomized to one of five groups: reperfusion after 20 min, 45 min, 60 min, 6 h or no reperfusion. Myocardial infarcts were created according to the methods of Connelly et al. (1985). In brief, anesthesia was induced and maintained with halothane and a thoracotomy was performed in the left 4th intercostal space. The

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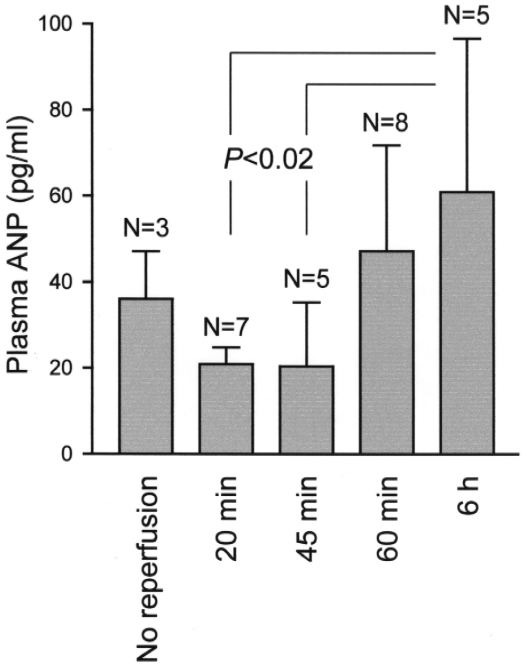

Fig. 1. Plasma ANP concentration for reperfusion and no reperfusion groups. The results are shown as means ± standard deviation. Analysis of variance (ANOVA) followed by the Tukey post hoc test was applied across all groups. Level of significance was $P < 0.02$.

pericardium was incised and an obtuse marginal branch of the left circumflex artery was ligated with 4-0 silk 2–3 mm below the atrial appendage. The suture was either released to permit reperfusion at the appropriate time or remained permanently ligated. Reperfusion was confirmed by a fall in ST segment elevation on the electrocardiogram. 10–15 days after recovery animals were re-anesthetized and 50 ml of blood extracted via cardiac puncture, prior to euthenasia by pentibarbitone overdose. The heart was removed, washed in ice cold saline and processed to paraffin. Sections from the apex, mid myocardium, i.e., papillary muscle level and base were stained with a trichrome stain and scanned into a PC computer. Using an image analysis software package (Image-Pro Plus), the percentage of the left ventricle infarcted was calculated. Sections at the level of the papillary muscle were also used to derive infarct expansion and remodeling indices (Eaton and Bulkley, 1981; Hochman and Choo, 1987). Blood collected was placed into heparinized tubes, chilled and centrifuged immediately. The plasma was then frozen and stored at −20°C for no longer than 6 months. Plasma ANP levels were measured without extraction of plasma via the radioimmunoassay method of Cohen et al. (1996).

Fig. 1 shows a histogram of the average plasma ANP levels obtained for each of the treatment groups during the late healing phase of the infarct (between 10 and 15 days post-infarction). Plasma ANP levels for the 6 h late reperfusion group were significantly greater ($P < 0.02$) than for the early reperfusion groups at 20 and 45 min. The ANP levels obtained for the 60 min reperfusion group and the no reperfusion group were intermediate between the early and late reperfusion groups, but were not statistically significantly different from either group. The pooled ANP concentrations were not significantly correlated with infarct size, infarct expansion or ventricular remodeling.

These results show that late reperfusion of the infarct related artery in a rabbit model of myocardial infarction is associated with increased circulating plasma ANP levels during the late healing phase of the myocardial infarct. Additionally the level of ANP following late reperfusion is significantly higher compared to early reperfusion. Thus, the elevated levels of ANP associated with late reperfusion compared to early reperfusion may act to facilitate diuresis and hence reduce pre-load and cardiac failure in affected patients.

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