Effect of atrial natriuretic peptide on left ventricular remodelling in patients with acute myocardial infarction

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Atrial natriuretic peptide (ANP) is a member of the natriuretic peptide family that exerts various biological effects via acting on the receptor-guanylyl cyclase system, increasing the content of intracellular cyclic guanosine monophosphate (cGMP). ANP was first identified as a diuretic/natriuretic and vasodilating hormone, but subsequent studies revealed that ANP has a very important function in the inhibition of the renin–angiotensin–aldosterone system (RAAS), endothelin synthesis, and sympathetic nerve activity. Evidence is also accumulating from recent work that ANP exerts its cardioprotective functions not only as a circulating hormone but also as a local autocrine and/or paracrine factor. ANP inhibits apoptosis and hypertrophy of cardiac myocytes, and inhibits proliferation and fibrosis of cardiac fibroblasts. Reperfusion of the ischaemic myocardium by percutaneous coronary intervention (PCI) reduces the infarct size and improves left ventricular (LV) function in patients with acute myocardial infarction (AMI). However, the benefits of PCI in AMI are limited by reperfusion injury. Animal studies have shown that ANP inhibits ischaemia/reperfusion injury, and reduces infarct size. We and others have recently shown that the intravenous administration of ANP inhibits RAAS, sympathetic nerve activity and reperfusion injury, prevents LV remodelling, and improves LV function in patients with AMI. ANP has a variety of cardioprotective effects and is considered to be a very promising adjunct drug for the reperfusion therapy in patients with AMI.

Keywords Atrial natriuretic peptide • Myocardial infarction • Remodelling

Introduction

Acute myocardial infarction (AMI) constitutes a major public health problem, not only in western countries but increasingly in developing countries.1 An estimated 1.1 million Americans will have a new or recurrent AMI per year, and many survivors will experience the progression to heart failure and death.2 Reperfusion of the ischaemic myocardium by percutaneous coronary intervention (PCI) reduces the infarct size and improves left ventricular (LV) function, both of which contribute to an improved clinical outcome in patients with AMI. In-hospital death from AMI decreased from 20–30 to 5–10% over the last 30 years.3 However, the increased survival rate resulted in the increased incidence of cardiovascular events, such as congestive heart failure and cardiac arrhythmias, after AMI. In some patients who undergo reperfusion therapy, reperfusion per se adversely leads to tissue damage known as ischaemia/reperfusion injury.4 The importance of limiting myocardial ischaemia/reperfusion injury and infarct size has been appreciated for many years. Hundreds of experimental interventions have been reported to protect the ischaemic myocardium or ischaemia/reperfusion injury in experimental animals, while adjunct therapy targeting the reduction of infarct size following AMI has not been established.2,5–7 Recent clinical trials focusing on the inhibition of inflammation with anti-C56 and anti-CD187,8 antibodies suggest that decreasing inflammation alone is insufficient in limiting reperfusion injury.

It is now recognized that reperfusion injury results from several complex and independent mechanisms that involve the production of reactive oxygen species, alterations in intracellular calcium handling, microvascular and endothelial cell dysfunction, myocardial...
stunning/apoptosis, and activation of neutrophils; reperfusion injury leads to the expansion of infarct area, LV remodelling, and LV dysfunction. The activation of neurohormonal factors is also known to be involved in the progression of myocardial stunning and LV remodelling. It is known that plasma norepinephrine concentrations affect the morbidity and mortality of patients with AMI.

Atrial natriuretic peptide (ANP) is a member of the natriuretic peptide family that has a variety of biological effects as a circulating hormone including diuresis, natriuresis, vasodilation, and inhibition of aldosterone synthesis, renin secretion, and sympathetic nerve activity. ANP thereby plays an important role in regulating blood pressure (BP) and blood volume. It is now known that ANP also acts as a local hormone in the heart.

In this review, we focus on the cardioprotective effects of ANP, and the therapeutic efficacy of ANP for the prevention of reperfusion injury and LV remodelling in patients with AMI.

### Natriuretic peptide family

The natriuretic peptide family includes three members: Atrial (A-type) natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). These are ligands for three receptors: NPR-A (also referred to as GC-A), NPR-B (also referred to as GC-B), and clearance receptor (C-receptor).

Human ANP was first identified from human atria in 1984 by Kangawa and Matsuo. They also isolated BNP and CNP from porcine brain. Later studies have revealed that ANP and BNP are synthesized mainly in the cardiac atrium and ventricle, respectively, whereas CNP is synthesized in endothelial cells, chondrocytes, and brain and acts as a local factor. Both ANP and BNP bind specifically to NPR-A, whereas CNP is a selective ligand for NPR-B. NPR-A and NPR-B are members of the membrane-bound guanylyl cyclase family, and natriuretic peptides exert biological activities via increasing intracellular cyclic guanosine monophosphate (cGMP) content.

ANP was originally identified as a diuretic/natriuretic and vasodilating hormone. Several investigators have reported that ANP dilates both arteries and veins in vivo, and decreases BP and enhances urine volume in rats and dogs. In humans, intravenous injection of human ANP also decreased BP, and increased urine volume. These results suggest that ANP and BNP play an important role in the regulation of vascular tone and water homeostasis. Subsequent studies have revealed that ANP and BNP exert also very important effects on inhibition of the renin–angiotensin–aldosterone system (RAAS), and sympathetic nerve activity. In fact, these peptides improve haemodynamics and congestion in patients with acute heart failure, and also counterbalance the neurohormonal activation underlying the decompensation of congestive heart failure. Recombinant human ANP and BNP have been approved as drugs for treating acute decompensated heart failure in Japan, and in the United States, Switzerland, and Israel, respectively.

It is now known that ANP exhibits a wide range of physiological effects including anti-fibrosis, anti-hypertrophy, anti-inflammation and inhibition of sympathetic nerve activity, RAAS, and endothelin synthesis (Table 1). As described in the previous section, reperfusion injury causes a variety of deleterious effects on the heart. ANP has a variety of biological effects to counter these various phenomena.

### Cardioprotective effects of atrial natriuretic peptide

As described in the previous section, reperfusion injury causes a variety of deleterious effects on the heart. ANP has a variety of biological effects to counter these various phenomena.

### Effect of atrial natriuretic peptide on renin–angiotensin–aldosterone system and endothelin synthesis

The process involved in the progression from AMI to LV dysfunction and heart failure include the development of myocardial stunning/apoptosis, LV remodelling, and acute and sustained neurohormonal activation. Previous studies have demonstrated that angiotensin II, aldosterone, and endothelin-1 each play a role in promoting structural remodelling of the myocardium. It is well known that ANP inhibits renin release and aldosterone synthesis in the kidney and adrenal gland, respectively. Recently, it has been reported that aldosterone is also produced in the failing or hypertensive human ventricle and may participate in the progression of cardiac fibrosis and cardiac failure. Ito et al. reported that ANP inhibits mRNA expression of CYP11B2, aldosterone synthase, in cardiac myocytes. ANP also inhibits endothelin-1 synthesis in endothelial cells.

It has been reported that infusion of ANP significantly decreases plasma concentrations of aldosterone, angiotensin II, and/or endothelin-1 in patients with AMI or patients undergoing cardiac surgery.

### Effect of atrial natriuretic peptide on sympathetic nerve activity

Sympathetic hyperactivity not only increases electrical instability of the myocardium, but also is responsible for an increase in platelet aggregation, coronary vasoconstriction, and higher wall stress. Previous studies have found that increased sympathetic activity is
associated with a high risk of malignant ventricular arrhythmias during myocardial ischaemia.\(^{35,36}\)

It has been reported that intravenous administration of ANP decreases renal sympathetic nerve activity and splanchnic nerve activity in anaesthetized rats.\(^{21}\) Power spectral analysis of heart rate (HR) variability is known as a marker of sympatho-vagal interaction in humans.\(^{37}\) Kosuge et al.\(^{38}\) investigated the effects of ANP and nitroglycerin (NTG) on BP, HR, plasma renin activity, and HR variability assessed from surface electrocardiographic data using spectral analysis, in patients with anterior AMI. NTG infusion (1.2 ± 0.2 μg/kg/min) and ANP infusion (0.05 ± 0.01 μg/kg/min) similarly decreased BP. NTG infusion increased HR, plasma renin activity, and the low- to high-frequency power ratio, and decreased high-frequency power. However, ANP infusion did not affect either HR or plasma renin activity, but decreased the low- to high-frequency power ratio and increased high-frequency power.\(^{38}\) Because the high-frequency power is usually used as an indicator of parasympathetic nerve activity, whereas the low- to high-frequency power ratio has been used as an indicator of sympathetic nerve activity,\(^{38}\) it is believed that ANP infusion augments parasympathetic nerve activity but does not stimulate sympathetic nerve activity.

Abramson et al.\(^{39}\) investigated the effect of ANP on muscle sympathetic nerve activity (MSNA) in patients with heart failure. Fifteen patients with dilated cardiomyopathy received intravenous ANP (50 μg bolus, then 0.05 μg/kg/min, intravenous infusion) or NTG (8 mg/min). During each infusion, MSNA, BP, central venous pressure (CVP), and HR were recorded before and during lower body negative pressure (LBNP) at −6 and −12 mmHg; NTG and ANP caused similar, significant reductions in CVP and diastolic BP, although resting MSNA did not increase with either infusion. LBNP at −6 mmHg only lowered the CVP but not BP, however, LBNP at −12 mmHg caused significant reductions in both CVP and BP. These effects of non-hypotensive and hypertensive LBNP on CVP and BP were similar during ANP and NTG infusions, yet MSNA was lower both before and during LBNP during ANP infusion (P < 0.02). Non-hypotensive LBNP increased MSNA during NTG infusion (133 ± 68 Units, P < 0.001), but not during ANP infusion (24 ± 23 Units). These observations support the concept that ANP exerts a sympatho-inhibitory action.

We also evaluated the effect of ANP on cardiac sympathetic nerve activity in patients with decompensated acute heart failure.\(^{40}\) A total of 28 patients were assigned to receive intravenous ANP, while the remaining 28 patients continued their established drug regimen. ANP was infused continuously for over 96 h at 0.025 μg/kg/min. Four weeks after treatment, LV volume and cardiac function evaluated by echocardiography were improved significantly by ANP infusion [LV end-diastolic volume, from 184 ± 36 to 179 ± 38 mL in the non-ANP group (P = NS) vs. from 186 ± 42 to 174 ± 48 mL in the ANP group (P < 0.05), LV ejection fraction (LVEF), from 31 ± 8 to 32 ± 7% in the non-ANP group (P = NS) vs. from 32 ± 9 to 36 ± 7% in the ANP group (P < 0.05)].

Myocardial imaging with \(^{123}\)I-metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with congestive heart failure.\(^{41,42}\) An association between the myocardial norepinephrine concentration and \(^{123}\)I-MIBG uptake in patients with congestive heart failure has been reported.\(^{42}\) \(^{123}\)I-MIBG imaging was performed 3 weeks after treatment, using a previously described method.\(^{43}\) The total defect score (TDS) was significantly lower, the heart/mediastinum count (H/M) ratio was significantly higher, and washout rate (WR) was significantly lower in the ANP treated group than in the non-ANP group (Table 2). The WR is known to reflect cardiac sympathetic nerve activity, whereas the \(^{123}\)I-MIBG uptake (i.e. TDS or H/M ratio) to reflect cardiac sympathetic nerve integrity.\(^{44}\)

Therefore, we concluded that intravenous administration of ANP can not only reduce cardiac sympathetic nerve activity, but also enhance cardiac sympathetic nerve integrity in patients with decompensated acute heart failure.\(^{40}\) Moreover, in this study,\(^{40}\) haemodynamic measurements (right atrial pressure, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure) evaluated by Swan-Ganz catheter at 2 weeks after treatment were similar in both the ANP group and non-ANP group. Thus, we speculated that the ANP treatment can ameliorate cardiac sympathetic nerve function compared with the other established therapies even if haemodynamic effects were similar. Furthermore, because previous reports suggested that inhibition of the RAAS can reduce cardiac sympathetic nerve activity and enhance cardiac sympathetic nerve integrity in patients with heart failure,\(^{45,44}\) the inhibitory effect of ANP on RAAS may have beneficial effects on cardiac sympathetic nerve activity.

### Table 2 Cardiac 123I-MIBG scintigraphic findings 3 weeks after ANP treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ANP group (n = 28)</th>
<th>Non-ANP group (n = 28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total defect score</td>
<td>30 ± 9</td>
<td>38 ± 9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>H/M ratio</td>
<td>1.86 ± 0.21</td>
<td>1.62 ± 0.23</td>
<td>0.0001</td>
</tr>
<tr>
<td>Washout rate (%)</td>
<td>42 ± 12</td>
<td>49 ± 12</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are the mean ± SD. The differences between ANP and non-ANP group were evaluate by ANOVA.

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### Effect of atrial natriuretic peptide on inflammation

Reperfusion is a potent stimulus for leucocyte activation and production of reactive oxygen species, which leads to coronary endothelial injury and microvascular dysfunction.\(^{4}\) Recently, it was shown that ANP reduces the activation of NF-kappa B and inhibits the secretion of inflammatory mediators, such as TNF-alpha and IL-1beta in macrophages.\(^{45}\) Another study showed that ANP significantly inhibits superoxide, lysozyme, and matrix metalloproteinase-9 release in activated neutrophils, and ANP limits neutrophil adhesion to hypoxic endothelial cells.\(^{46}\) Kato et al.\(^{47}\) recently reported that ANP infusion (0.025 μg/kg/min) for 96 h does not affect BP or HR, but improves diastolic function, and decreases plasma BNP, IL-1beta, and IL-6.
concentrations and increases IL-10 concentrations, in patients with chronic heart failure.

**Effect of atrial natriuretic peptide on endothelial dysfunction**

When exposed to cardiac ischaemia, endothelial cells develop changes in their structure, causing their margins to retract from each other; TNF-alpha is thought to play a role in the signal cascade that increases pathological endothelial permeability. ANP treatment is shown to abrogate the TNF-alpha induced increase in permeability. ANP also attenuates alterations in endothelial cell morphology and stress fibre formation. Matsumura et al. reported that ANP and BNP exert protective effects against the neutrophil-induced endothelial cytotoxicity. These results suggest that ANP could inhibit the inflammatory process, oxidative stress, and endothelial injury upon reperfusion.

**Effect of atrial natriuretic peptide on coronary circulation**

Activation of neutrophils and release of proinflammatory cytokines, such as TNF-alpha and IL-1beta, result in the generation of reactive oxygen species, endothelial injury, and no-reflow phenomenon after reperfusion therapy. As mentioned above, ANP inhibits cytokine release from leucocytes and prevents endothelial damage. In conscious dogs, ANP dilates coronary resistance vessels and increases coronary blood flow. Foreman et al. showed that ANP causes an increase in coronary collateral blood flow in dogs. In humans, Egashira et al. reported that ANP (0.03 μg/kg/min) causes a dilation of large epicardial coronary arteries and coronary resistance vessels, suggesting that ANP can improve ischaemia by preserving coronary circulation. It has also been reported that intra-coronary infusion of ANP (0.025 μg/kg/min) significantly increases the collateral blood flow in patients with coronary angioplasty, and ameliorates myocardial ischaemia.

These results suggest that ANP inhibits the activation of RAAS, endothelin synthesis and sympathetic nerve activity, and suppresses the inflammatory signals. ANP also preserves endothelial function and coronary blood flow. These effects could contribute to the suppression of reperfusion injury and LV remodelling after PCI in patients with AMI by ANP. On the other hand, recent gene targeting studies focusing on ANP or NPR-A have clarified the direct inhibitory action of ANP and BNP on cardiac hypertrophy and fibrosis. For example, NPR-A deficiency in mice leads to marked cardiac hypertrophy and ANP deficiency results in exaggerated hypertrophy and remodelling after pressure overload, suggesting that the endogenous ANP/NPR-A system may have an inhibitory role in the regulation of cardiac cell growth.

**Effect of atrial natriuretic peptide on apoptosis of cardiac myocytes**

The dominant cause of heart failure after AMI is regional loss of myocardium due to ischaemia and ischaemia/reperfusion injury that leads to cardiomyocyte necrosis and apoptosis. During ischaemia/reperfusion in rodents and humans, 5–30% of cardiac myocytes in the area at risk undergo apoptosis within 16 h. Kato et al. reported that pathophysiological and therapeutic concentrations of ANP (0.1–1 nM, ca. 300–3000 pg/mL) significantly inhibits apoptosis in rat cardiac myocytes and this effect is mediated by the increase in cGMP followed by activation of the Akt/PI3K pathway.

**Effect of atrial natriuretic peptide on cardiac hypertrophy**

Pathophysiological mechanisms leading to LV dilation after an AMI include early thinning and stretching of the infarcted segment (i.e. infarct expansion) and hypertrophy of the non-infarcted myocardium. Such LV dilation may adversely affect subsequent cardiac function, leading to heart failure and death.

Calderone et al. investigated the effect of exogenously administered ANP on the cardiac hypertrophy induced by norepinephrine. ANP, as well as a nitric oxide (NO) donor and 8-bromo-cGMP, decrease the norepinephrine-stimulated protein synthesis in rat cardiac myocytes. ANP also inhibits protein synthesis induced by the Ca2+/ channel agonist, BAY K8644. These findings indicate that ANP and NO can attenuate the effects of norepinephrine on the growth of cardiac myocytes via a cGMP-mediated inhibition of Ca2+/ influx induced by norepinephrine. Similarly, ANP inhibits angiotensin II or endothelin-1 induced hypertrophy in rat cardiac myocytes via increases in cGMP and inhibition of mitogen-activated protein kinase signalling. Horio et al. investigated the effects of a specific antagonist of natriuretic peptide receptors, HS-142-1, on the expression of fetal-type contractile protein genes as well as protein synthesis in cultured cardiac myocytes. HS-142-1 increased the basal and phenylephrine-stimulated protein syntheses. This antagonist also induces significant increases in the size of myocytes. These results suggest that endogenous ANP inhibits the cardiac myocyte hypertrophy as an autocrine factor.

**Effect of atrial natriuretic peptide on cardiac fibrosis**

Cardiac fibrosis is known to be a major component of LV remodeling along with cardiac hypertrophy in patients after AMI. In rat cardiac fibroblasts, ANP inhibits DNA synthesis stimulated by angiotensin II or endothelin-1. In accordance with this observation, myocyte-conditioned medium, as well as exogenous ANP, inhibits collagen synthesis in cardiac fibroblasts and this effect is suppressed by the ANP antagonist, HS-142-1, suggesting that endogenous ANP released from cardiomyocytes inhibits collagen synthesis. Thus, ANP secreted by myocytes inhibits the proliferation and fibrosis of cardiac fibroblasts as a paracrine factor.

**Metabolic effect of atrial natriuretic peptide in cardiac myocytes**

Cardiac cells usually use fatty acids as metabolic substrates. However, they revert to glucose consumption during hypoxia to maintain myocardial viability. Clinical and experimental studies have shown that increased glucose uptake during acute myocardial ischaemia is associated with preserved cardiac function and decreased release of myocardial enzymes. In rat neonatal cardiac myocytes, hypoxia significantly increased glucose uptake, and this was stimulated by the addition of ANP, although ANP...
ANP inhibits LV remodelling in patients with AMI

Atrial natriuretic peptide in myocardial ischaemia/reperfusion—animal studies

Ischaemia/reperfusion model in isolated hearts

Sangawa et al.\(^7\) investigated the effect of ANP on cardiac function after ischaemia/reperfusion in isolated rat hearts. Rat hearts were subjected to 15 min of global ischaemia followed by 15 min of reperfusion, and ANP was added at the time of reperfusion. In the ANP treated group, the recovery of cardiac output was significantly better than in the control group (82.1 ± 9.8% in the ANP group, 61.8 ± 6.8% in the control group, \(P < 0.01\)) with a similar trend towards recovery of coronary flow (90.7 ± 8.5% in the ANP group, 79.3 ± 11.8% in the control group). Improved cardiac function was closely related to a significant increase in post-ischaemic cGMP release. Similar results were obtained in the isolated rabbit heart.\(^7\) Rabbit hearts were subjected to 30 min of ischaemia followed by 120 min of reperfusion. ANP treatment just before reperfusion significantly reduced infarct size (12.5 ± 2.0% in the ANP group, 31.5 ± 2.4% in the control group, \(P < 0.001\)). The effect was mimicked by an activator of cGMP-dependent protein kinase.

Ischaemia/reperfusion model in vivo

The effect of ANP on ischaemia/reperfusion injury was evaluated in dogs subjected to a 30-min coronary artery occlusion and 60-min reperfusion.\(^7\) ANP (0.1 \(\mu\)g/kg/min) or a 5% glucose solution was injected intravenously during occlusion and reperfusion. There were no significant differences in haemodynamic parameters during ischaemia and reperfusion between the groups. In the ANP treated group, the prevalence of ventricular extrasystoles within 10 min after reperfusion significantly decreased (22% in the ANP group, 100% in the control group, \(P < 0.01\)). No dogs in the ANP group had ventricular fibrillation (0% in the ANP group, 25% in the control group). The ATP content in the inner layers of the ischaemic myocardium was significantly higher in the ANP group than in the control group. The plasma concentration of cGMP was increased 8-fold during ANP infusion. Since cGMP is thought to modulate \(\text{Ca}^{2+}\) efflux by stimulating \(\text{Na}^+ / \text{Ca}^{2+}\) exchange and the ATP-dependent \(\text{Ca}\) pump,\(^7\) the authors suggested that ANP might inhibit \(\text{Ca}\) overload of the myocardial cells via cGMP-dependent mechanisms.

In another dog model, either saline (control) or human ANP was infused intravenously (0.1 \(\mu\)g/kg/min), starting 30 min before and continuing 10 min during a 25-min occlusion of the left anterior descending coronary artery.\(^7\) The elevation in LV end-diastolic pressure was significantly less in the ANP group than in the control group (9.0 ± 0.9 mmHg in the ANP group, 12.2 ± 0.8 mmHg in the control group, \(P < 0.05\)). Compared with the control group, ANP decreased the number of ventricular premature beats (26 ± 12 in the ANP group, 416 ± 87 in the control group, \(P < 0.05\)), the number of episodes of ventricular tachycardia (VT) (0.7 ± 0.3 in the ANP group, 12.4 ± 4.2 in the control group, \(P < 0.05\)), and the incidence of VT (45% in the ANP group, 100% in the control group, \(P < 0.05\)) and ventricular fibrillation (18% in the ANP group, 57% in the control group, \(P < 0.05\)) during occlusion. The severity of myocardial ischaemia, as assessed by changes in the epicardial ST-segments and the degree of inhomogeneity, was also significantly less marked in dogs given ANP. Based on these results, ANP would be expected to prevent reperfusion injury and LV remodelling by the attenuation of early neurohormonal and inflammatory activation as well as having direct protective effects on cardiac cells (Figure 1).

Atrial natriuretic peptide treatment after reperfusion therapy in patients with acute myocardial infarction—clinical findings

In the acute phase of AMI, NTG has been reported to have a favourable effect in preventing LV remodelling.\(^7\) However, NTG may stimulate the RAAS despite its beneficial haemodynamic effect.\(^3\) In contrast, ANP has a wide range of cardioprotective effects, including the inhibition of RAAS and sympathetic nerve activity, as described in the previous sections. We and others have investigated the efficacy of intravenous ANP in patients with AMI.\(^3,27,67\) These studies are summarized below.
Hayashi et al.\textsuperscript{72} evaluated the effect of ANP compared with NTG on LV remodelling after a first anterior AMI. Sixty patients with a first anterior AMI, who received successful reperfusion therapy within 24 h of the onset of chest pain, were divided randomly into two groups; ANP \((n = 30)\) or NTG \((n = 30)\) after undergoing direct PCI. ANP \((0.025 \mu g/kg/min)\) or NTG \((0.4 \mu g/kg/min)\) infusion was continued for \(\sim 2.5\) days \((61.5 \pm 5.6\) h in the ANP group, \(64.0 \pm 4.9\) h in the NTG group). There was no difference in the baseline characteristics or LVEF between the two groups \((46.9 \pm 1.0\%\) in the ANP group, \(46.8 \pm 1.3\%\) in the NTG group). There were also no differences in haemodynamic changes during the infusion periods. LVEF was improved significantly after 1 month compared with the baseline value in both groups, although LVEF was more improved in the ANP group than in the NTG group \((54.6 \pm 1.3\%\) in the ANP group, \(50.8 \pm 3.1\%\) in the NTG group, \(P < 0.05\)). LV enlargement was prevented in the ANP group \((LV\text{ end-systolic volume index}, 45.6 \pm 1.8–41.0 \pm 2.1\text{ mL/m}^3, P < 0.05)\), but not in the NTG group \((46.3 \pm 2.8–51.1 \pm 3.0\text{ mL/m}^3)\). During the infusion, ANP decreased the plasma concentrations of aldosterone, angiotensin II, and endothelin-1 compared with NTG. These findings indicate that in patients with a first anterior AMI, an ANP infusion can prevent LV remodelling better than NTG, and effectively suppresses neurohormonal activation after reperfusion.

In another study, Kuga et al.\textsuperscript{76} evaluated the effects of ANP on myocardial reperfusion injury and LV remodelling. Nineteen patients presenting within \(12\) h of a first AMI underwent intracoronary injection of \(25 \mu g\) of ANP immediately after coronary angioplasty, combined with intravenous infusion of \(0.025 \mu g/kg/min\) of ANP initiated on admission and continued for \(1\) week (ANP group). Eighteen similar patients were treated with saline (control group). The incidences of reperfusion injury including premature ventricular contraction, VT and/or fibrillation, in the ANP group were significantly less than in the control group after coronary angioplasty. The incidence of ST-segment elevation \((ST > 50\%)\) in the ANP group was also significantly less than in the control group (Table 3).

LVEF was significantly greater and LV end-diastolic volume index \((\text{LVEDVI})\) was significantly less 6 months after coronary angioplasty. The incidence of ST-segment elevation \((ST \geq 0.1\text{ mV})\) in the ANP group was significantly less than in the control group after coronary angioplasty. The incidence of VT/VF (sustained VT/VF) was significantly less than in the control group after coronary angioplasty.

**Table 3** Effect of ANP administration on the number of premature ventricular contractions, the incidence of ventricular tachycardia and/or ventricular fibrillation and the incidence of persistent ST elevation \((ST > 50\%)\)

<table>
<thead>
<tr>
<th></th>
<th>ANP group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PVC (beats/10 min)</td>
<td>6 \pm 5</td>
<td>194 \pm 78*</td>
</tr>
<tr>
<td>Incidence of VT/VF (%)</td>
<td>0</td>
<td>33**</td>
</tr>
<tr>
<td>Incidence of ST &gt;50 (%)</td>
<td>0</td>
<td>44**</td>
</tr>
</tbody>
</table>

*\(P < 0.01\) vs. ANP group by unpaired Student’s \(t\)-test.
**\(P < 0.05\) vs. ANP group by Fisher’s exact test.
1 PVC, premature ventricular contractions; VT/VF, ventricular tachycardia and/or ventricular fibrillation.

Recently, we investigated the effects of ANP on LV remodelling and cardiac sympathetic nerve activity in patients presenting with a first anterior AMI in a single-centre, prospective, double-blinded study.\textsuperscript{77} Fifty patients presenting within \(6\) h of their first anterior AMI were assigned randomly to receive ANP \((0.025 \mu g/kg/min, n = 25)\) or isosorbide dinitrate \((\text{ISDN}, 0.67 \mu g/kg/min, n = 25)\). After haemodynamic stability was assured, the ANP or ISDN infusion was started and continued for \(56 \pm 15\) or \(59 \pm 16\) h, respectively \((range: 48–96\) h). There were no differences in the two groups with respect to clinical characteristics, initial myocardial damage \((area at risk)\) defined by \(^{99m}\text{Tc-pyrophosphate scintigraphy, and in-hospital use of medications. ANP treatment significantly reduced the incidence of reperfusion injury compared with ISDN treatment (ST-segment re-elevation: 20\% in the ANP group, 35\% in the ISDN group, \(P < 0.05\); reperfusion arrhythmia: 28\% in the ANP group, 48\% in the ISDN group, \(P < 0.05\)). The TDSs, determined by \(^{123}\text{I-MIBG scintigraphy, were significantly lower in the ANP group than in the ISDN group (27 ± 7 in ANP the group, 32 ± 6 in the ISDN group, \(P < 0.01\)), indicating that ANP increases the amount of salvaged myocardium after PCI and inhibits the expansion of the infarct area. ANP also inhibits LV remodelling and improves LV function 2 weeks after PCI \((\text{LVEDVI: 85.5 ± 28.5 mL in the ANP group, 106.3 ± 39.4 mL in the ISDN group, \(P < 0.05\); LVEF: 47.9 ± 10.2\% in the ANP group, 41.5 ± 11.8\% in the ISDN group, \(P < 0.05\)). Moreover, in the \(^{123}\text{I-MIBG findings, the TDS and WR were significantly lower; the H/M ratio was significantly higher in the ANP treated group than in the ISDN group (Figure 2). Because the WR reflects cardiac...
sympathetic nerve activity, and the $^{123}$I-MIBG uptake reflects cardiac sympathetic nerve integrity.\textsuperscript{41} Our results suggested that intravenous ANP can reduce cardiac sympathetic nerve activity and reduce loss of sympathetic innervation associated with ischaemia or reperfusion injury in patients with AMI.

Although these studies were all small single-centre studies, they clearly and consistently indicated that a low dose (0.025 \(\mu\)g/kg/min) of ANP significantly ameliorates reperfusion injury and cardiac remodelling, and improves LV function in patients with AMI at least in part via the inhibition of the early activation in neurohormonal factors.

Recently, the cardioprotective effects of ANP in patients with AMI were confirmed by a large multi-centre randomized trial, named J-WIND (Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage by ANP or nicorandil).\textsuperscript{78–80} The J-WIND studies were composed of two individual trials. In one trial, patients were randomized in a blinded manner to human ANP infusion (0.025 \(\mu\)g/kg/min for 3 days; \(n=277\)) or 5% glucose infusion (\(n=292\)). In the other trial, the effect of nicorandil was investigated. The ANP trial was conducted in 27 hospitals in Japan. The primary endpoint of infarct size as assessed by area under the curve for creatine kinase release was 14.7% lower with ANP compared with control ($P=0.016$). Likewise, the other primary endpoint, LVEF, was increased 5.1% with ANP compared with control ($P=0.024$). Among the secondary endpoints, reperfusion injury was reduced by 25.9% with ANP compared with control ($P=0.019$). There was no difference in mortality or the composite clinical endpoint between ANP and control. The composite of cardiac death or heart failure was lower with ANP than control (hazard ratio 0.27, $P=0.011$).

Thus, the cardioprotective effects of ANP in basic studies and small clinical trials were reproduced and confirmed by a multi-centre, randomized, prospective trial. Although the J-WIND trial was not large enough to evaluate mortality and/or morbidity after AMI, it is noteworthy that ANP reduced cardiac death and/or heart failure by >70% over control. It should be also noted that these effects were obtained by a relatively low dose of ANP (0.025 \(\mu\)g/kg/min) without significantly affecting systemic BP. The treatment period of \(\approx3\) days in these studies coincides with the duration of the acute activation of neurohormonal factors and early cardiac cell death after reperfusion therapy.\textsuperscript{32,81–83}

### Conclusions

In conclusion, ANP has a variety of biological actions that protect cardiac tissue from ischaemia/reperfusion injury. We and others have shown that ANP can inhibit early activation of neurohormonal factors and inflammation after reperfusion therapy, and also reverse arrhythmias, apoptosis of cardiac myocytes and endothelial cells, and limit infarct size and LV remodelling, thereby improving LV function in animal models with ischaemia/reperfusion injury and in patients with AMI. Findings from a recent multi-centre study also suggest that ANP can reduce subsequent re-hospitalization or death due to heart failure. These cardioprotective effects of ANP were observed at a low dose of ANP without a large effect on systemic BP in patients with AMI.

On the other hand, recent clinical studies have suggested that stem cell therapy can contribute to the regeneration of infarcted myocardium and enhance neovascularization of ischaemic myocardium, resulting in sustained improvement in cardiac function.\textsuperscript{84,85} However, stem cell therapy is generally very expensive, and the protocols and safety of this cell therapy have not yet been established. Therefore, we believe that ANP provides a very promising, easy, and safe adjunct therapy in patients with AMI.

### Conflict of interest: none declared.

### References


