Review

Roles of atrial natriuretic peptide and its therapeutic use

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Summary Since the discovery of atrial natriuretic peptide (ANP), there has been tremendous progress in our understanding of the physiologic and pathophysiologic, diagnostic, and therapeutic roles of ANP. The diagnostic application of ANP and brain natriuretic peptide (BNP) has been reviewed by many investigators, and meta-analyses of therapeutic use of BNP were reported from the USA. However, there are few reviews concerning the therapeutic use of ANP in patients with various conditions. Therefore, this review focuses on the recent clinical evidence of ANP in therapeutic use and experimental data that rationally support the therapeutic use of ANP.

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Introduction

Since the discovery of atrial natriuretic peptide (ANP) at the end of 1983 [1] and the beginning of 1984 [2], major advances have taken place in our understanding of the physiology and pathophysiology of the heart. Before the discovery of ANP, the heart was believed to function solely for the delivery of blood to all organs in the body; after ANP was elucidated, it became evident that the heart also regulates blood pressure, fluid volume, and electrolyte balance [3,4]. Therefore, the heart plays at least two major biological roles: a pumping function and an endocrine function.

During the past three decades, evidence accumulated that a number of hormones, paracrine factors, and intracellular signaling molecules are involved in heart development, cardiac contraction, cardiac hypertrophy, and heart failure (HF). Among these biologically active substances, ANP and B-type natriuretic peptide (BNP) are the best-investigated molecules, and are now clinically used as diagnostic tools and therapeutic drugs in HF.

In 1995, the Ministry of Health and Welfare of Japan approved recombinant ANP (carperitide) for intravenous administration in patients with acute heart failure (AHF) and acutely decompensated heart failure (ADHF). However, the recombinant form of BNP (nesiritide) was not approved for therapeutic use in Japan. In contrast, in the USA, the Food and Drug Administration (FDA) approved nesiritide in 2001. Therefore, the clinical evidence for ANP has been compiled mainly in Japan, whereas the evidence for BNP is mainly from the USA. Several reviews and meta-analyses concerning BNP use were generated using data obtained in the USA [5–7]. In this context, this review focuses on recent clinical data regarding ANP as a therapeutic agent in several diseases, as well as experimental data from genetically engineered mice which may rationalize the clinical usefulness of ANP.

Discovery of natriuretic peptide (NP) family

The discovery of atrial-specific granules, which resemble the electron-dense granules observed in endocrine organs, by Kirsh [8] in 1956 marks one of the first milestones on the road of ANP research. In 1979, deBold [9] found that the number of atrial-specific granules is decreased by water deprivation and increased by salt loading, suggesting that atrial-specific granules contain a biologically active substance involved in volume regulation. At the end of 1983 and the beginning of 1984, a new peptide with 28 amino acid residues was isolated by deBold from rat atrial tissues [1], and by Matsuo and Kangawa from human atrial tissues [2]. The peptide was designated as ANP, and exhibits diuretic, natriuretic, and vasodilating activities. Following the discovery of ANP, Matsuo and Kangawa also isolated brain natriuretic peptide, or B-type natriuretic peptide (BNP) from the porcine brain in 1988 [10], and C-type natriuretic peptide (CNP) from the porcine brain in 1990 [11]. ANP is mainly synthesized in the atria and BNP in the ventricles; thus, ANP and BNP are cardiac hormones [12–14]. The expression of ANP and BNP is increased in cardiac hypertrophy in response to atrial or ventricular wall stress, respectively, as well as in HF. CNP is synthesized in endothelial cells, macrophages, neurons, and osteoblasts, although cardiac expression of CNP is low [3,4].

Biological actions of ANP and BNP

ANP and BNP bind their common receptor, guanylyl cyclase-A (GC-A), which is a membrane-type guanylyl cyclase, and leads to biological actions through a cGMP-dependent pathway (Table 1). Classically ANP and BNP possess diuretic, natriuretic, and hypotensive activity. ANP induces dilation of arteries and veins in an endothelium-independent manner. In vascular smooth muscle cells (SMCs), GC-A is expressed abundantly; binding of ANP or BNP produces cGMP and activates cGMP-regulated protein kinase I (cGKI) [15]. SMCs express both cGKIα and cGKIβ. Earlier reports showed that cGKI inhibits vascular smooth muscle contraction by multiple mechanisms, including the cGKIα-containing cGMP kinase substrate (IRAG), the cGKIα-regulator of G protein signaling subtype 2 (RGS2), and the cGKIα/myoosin light chain phosphatase (MLCP) signaling pathway. cGKIβ/IRAG signaling inhibits release of Ca++ from sarcoplasmatic reticulum (SR). cGKIα binds, phosphorylates, and activates RGS2, which terminates signaling by Gq-coupled receptors for contractile agonists [16].
and water excretion\[18\]. The natriuretic effect of ANP is arterioles. Thus, ANP has dose-dependent effects of solute and, in some cases, from slight constriction of efferent pressure that results from dilation of afferent arterioles (GFR) due to an elevation of glomerular capillary hydrostatic increased permeation of water and macromolecules through the endothelium into the interstitial space\[17\].

In the kidney, ANP increases the glomerular filtration rate (GFR) due to an elevation of glomerular capillary hydrostatic pressure that results from dilation of afferent arterioles and, in some cases, from slight constriction of efferent arterioles. Thus, ANP has dose-dependent effects of solute and water excretion [18]. The natriuretic effect of ANP is attributed almost entirely to cGMP-dependent inhibition of sodium reabsorption in the inner medullary connecting duct and chloride in the cortical collecting duct. ANP appears to coordinate myosin light chain phosphorylation and causes relaxation. Thus, these are the mechanisms of the acute depressor effect of ANP. However, recently Kuhn et al. [17] reported that the mechanisms of the chronic depressor effect of ANP are quite different from those of the acute effect. The chronic depressor effect is due to a decrease in intravascular volume resulting from increased permeation of water and macromolecules through the endothelium into the interstitial space [17].

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In addition to its vascular and renal function, ANP inhibits aldosterone secretion from cultured adreno-cortical cells. Clinically, when ANP is infused in healthy subjects and patients with HF, the plasma aldosterone concentration decreases promptly and returns after cessation of infusion.

### Roles of ANP and BNP: lessons from genetically engineered mice

#### Roles of ANP and BNP in blood pressure and cardiac remodeling

The physiological roles of ANP and BNP have been investigated using ANP knockout (KO) mice [19] and GC-A KO mice [20]. ANP KO mice exhibit salt-sensitive hypertension [19], but GC-A KO mice exhibit salt-insensitive hypertension with ventricular hypertrophy and fibrosis [20]. The reason for the phenotypic difference between ANP and GC-A KO mice remains unclear. Cardiac remodeling in GC-A KO mice is blood pressure-independent, and is almost completely inhibited by crossing with AT1 KO mice or treatment with angiotensin receptor blocker, suggesting that the GC-A signaling functionally antagonizes the AT1 signaling [21,22]. As mentioned above, cGKI binds directly to and phosphorylates/activates RGS2, which terminates cGKI G(q)-coupled receptor signaling in vascular smooth muscle [16]. Consistent with this, Tokudome et al. reported that cardiomyocyte-specific overexpression of RGS4, the major RGS protein in the cardiomyocytes, in GC-A-KO mice significantly reduced hypertrophy, cardiomyocyte size, and ventricular calcineurin activity [23]. Thus, the possible mechanism for the antagonistic action of ANP and BNP against angiotensin II may be explained by GC-A/cGKI/RGS4 interaction. Treatment with an aldosterone blocker, eplerenone, significantly improved ventricular hypertrophy and fibrosis [24]. Currently, it remains unclear how GC-A signaling interacts with other signaling pathways via a mineralocorticoid receptor.

The mechanism for hypertension in GC-A has been intensively investigated by Kuhn et al. using SMC- [25] or endothelial cell-(EC) [17] specific GC-A KO mice (Table 2). SMC-specific GC-A KO (SMC-GC-A KO) mice exhibit blood pressure equal to control mice (GC-Aflox/flox), but have no hypotensive response to exogenously administered ANP. In EC-specific GC-A KO (EC-GC-A KO), blood pressure is similarly elevated to the level in straight GC-A KO mice, but exogenous ANP injection significantly decreases blood pressure. Kuhn et al. [26] also proved that ANP enhances microvascular endothelial macromolecule permeability in vivo. These results clearly indicate that the mechanism for hypertension in GC-A KO mice involves an increase in intravascular volume resulting from the inhibition of permeation of the blood from the intravascular space to the extravascular space. It remains unknown which channels or transporters are involved in GC-A-mediated permeation in EC.

#### Roles of ANP and BNP in acute myocardial infarction

A number of experimental and clinical studies revealed that expression of ANP and especially BNP are increased in the infarct region of the ventricle. Plasma levels of ANP and BNP are also increased in the acute phase of acute myocardial infarction (AMI) in humans; plasma BNP increases especially rapidly, decreases within 24 h, increased again within 7 days and then decreases gradually [27]. When patients are treated with angiotensin-converting enzyme inhibitor, this second peak is obscured [28], suggesting that the second transient elevation of plasma BNP level is related to acute ventricular stress. Thus, ANP and BNP have some pathological roles in AMI as hormones and/or paracrine factors.

To investigate the roles of ANP and BNP in AMI, we generated permanent coronary occlusion models and ischemia reperfusion models in GC-A KO mice and BNP transgenic.

<table>
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<th>Table 2</th>
<th>Blood pressure profile in tissue specific GC-A KO mice.</th>
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<tr>
<td>BP</td>
<td>BP response to ANP</td>
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<tr>
<td>Floxed GC-A</td>
<td>→</td>
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<tr>
<td>Straight GC-A KO</td>
<td>↑</td>
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<tr>
<td>SMC-GC-A KO</td>
<td>→</td>
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<tr>
<td>EC-GC-A KO</td>
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GC-A, guanylyl cyclase-A; KO, knockout; BP, blood pressure; ANP, atrial natriuretic peptide; SMC, smooth muscle cell; EC, endothelial cell.
(BNP-Tg) mice. When GC-A KO and wild-type (WT) mice were subjected to permanent coronary ligation, the GC-A KO mice exhibited lower survival rate and more severe ventricular fibrosis and post-infarct hypertrophy than WT mice [29]. GC-A KO mice with AMI died within 7 days after ligation; a major cause of death was probably HF, because lung weight is significantly heavier in GC-A KO mice. Urine volume and urinary excretion of sodium decreased just after the operation in both genotypes of mice; GC-A KO mice recovered more slowly than WT mice, which may be related to the more severe HF in GC-A KO mice. Because GC-A KO mice are hypertensive, we investigated whether or not hydralazine treatment rescues the poor survival rate and ventricular remodeling in GC-A KO mice; however, this treatment rescued neither poor survival nor ventricular remodeling. Given that the phenotype of GC-A KO is almost blocked by crossing with mice lacking type 1 angiotensin receptor (AT1), we generated an AMI model in GC-A and AT1 double KO mice. The results were very interesting. Although chronic ventricular remodeling such as hypertrophy and fibrosis disappeared almost completely in double KO mice (Fig. 1B and C), the survival rate in double KO mice was the same as in GC-A KO mice (Fig. 1A) [29]. These findings suggest that chronic ventricular remodeling is AT1-dependent, but acute death is not AT1 dependent.

Therapeutic application of ANP in the acute phase may have some beneficial effects in AMI that cannot be replaced by angiotensin receptor blockers or angiotensin-converting enzyme inhibitors.

To determine whether GC-A signaling contributes to the extension of infarction in the very acute phase of AMI, we developed a model involving 30-min coronary artery ligation followed by 48-h reperfusion. Unexpectedly, infarct size assessed by triphenyltetrazolium chloride staining was significantly smaller in GC-A KO mice than WT mice. Histological examination revealed that neutrophils were less infiltrated into the infarct region, with lower expression levels of P-selectin in coronary artery endothelium in GC-A KO mice. P-selectin is involved in the infiltration of neutrophils, and plays key roles in reperfusion injury in myocardium; consistent with this, reperfusion injury is less severe in GC-A KO mice. Moreover, we confirmed that endothelial expression of P-selectin is transcriptionally promoted by NF-κB activation in which GC-A signaling is involved [30] (Fig. 2).

We also generated a permanent occlusion model in mice overexpressing the BNP gene under control of the serum amyloid protein A promoter, in which mice BNP is not overexpressed in the heart but in the liver, and BNP is constitutively secreted from the liver, resulting in high circulating BNP level of ~10 ng/ml. When AMI was generated in BNP-Tg
mice, BNP-Tg mice more frequently died ∼3 to 5 days after the occlusion due to ventricular free wall rupture, with more massive infiltration of neutrophils in the infarct region than WT mice. In BNP-Tg mice, higher expression of metalloproteinase-9 (MMP-9) was observed in infiltrated neutrophils by immunostaining and overactivation of MMP-9, and was confirmed by gelatin-zymography. This result suggests that activation of MMP-9 was related to the free wall rupture. BNP-Tg mice were rescued by treating with doxycycline, an inhibitor of MMP-9 [31].

Roles of ANP and BNP in renal diseases

To date, there has been no report describing the roles of ANP or BNP in kidney disease using genetic ablation models. Renal abnormalities in GC-A KO mice and ANP KO mice have not been described in earlier reports. In fact, we found neither macroscopic nor microscopic abnormalities in the kidney of GC-A KO mice, suggesting ANP/GC-A signaling does not play important roles in the development of the kidney. Endogenous expression levels of ANP and BNP genes in the kidney are quite low compared with those in the heart, whereas GC-A is abundantly expressed in the kidney. Therefore, ANP and BNP systems act as hormones rather than paracrine factors in the kidney. GC-A KO mice do not increase urination and sodium excretion in response to volume overload with iso-osmotic solution [20].

Kasahara et al. [32] investigated the effect of high levels of circulating BNP on glomerular injury induced by subtotal nephrectomy (two-thirds right renal resection and left renal resection) using BNP-Tg mice. Subtotal nephrectomy induced mild to moderate systemic hypertension, increased serum creatinine levels, and caused albuminuria together with remarkable glomerular hypertrophy and moderate mesangial expansion 16 weeks after operation in WT mice, relative to sham-operated mice. However, in BNP-Tg mice all these findings were lessened significantly. Although glomerular expression of transforming growth factor-β and fibronectin was also increased after subtotal nephrectomy in WT mice, the expression was less increased in BNP-Tg mice. The renal-protective effect of circulating BNP following glomerular injury was also reported for anti-glomerular basement membrane nephritis [33] and diabetic nephropathy [34].

Roles of ANP in angiogenesis

Recently, a new function for the NP/GC-A system—as regulator of angiogenesis of heart and skeletal muscle—was reported by two groups independently [35,36]. Vascular regeneration in response to hind limb ischemia was severely impaired in GC-A KO mice. EC-GC-A KO mice exhibited similar responses, but SMC-GC-A KO mice did not affect ischemic neovascularization. Bone marrow transplantation experiments showed that GC-A signaling did not influence mobilization of vascular progenitor cells from bone marrow. BNP expression was augmented in satellite cells within ischemic skeletal muscle, suggesting that local BNP elicits protective endothelial effects. Yamahara et al. [37] reported that neovascularization in response to hind-limb ischemia was more accelerated in BNP-Tg mice than in WT mice. These findings suggest the possibility that ANP is a potentially valuable therapeutic agent for stimulating angiogenesis in ischemic tissues.

Therapeutic use of ANP for heart diseases

Preclinical reports of ANP infusion

Given that ANP possesses diuretic, natriuretic, and vasodilating activities, cardiologists have hypothesized since its discovery that ANP might be useful for the treatment of HF. Preclinical investigations concerning the effect of ANP infusion in cardiac, renal, and hormonal functions in patients with congestive HF were reported in 1986 and 1987 by three groups of investigators, including us [38–40]. Although the reports were of small studies, the results from all three groups were similar and significant. In our report, ANP...
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infusion at a rate of 0.1 \( \mu g/kg/min \) significantly decreased pulmonary capillary wedge pressure and systemic vascular resistance, and increased stroke volume index. Thus, ANP improves cardiac function by altering loading conditions for the left ventricle. ANP infusion increases GFR and induces diuresis. A significant reduction in plasma levels of aldosterone was observed. Based on the preclinical data, ANP was licensed in Japan in 1995 for the treatment of AHF or ADHF. Japan was the first country in the world to approve the drug for this use. Today, ANP is commonly used in patients with AHF and ADHF, and its market share is the largest in the AHF and ADHF market. The total cost of ANP in 2009 in Japan was over 10 billion yen.

Therapeutic use of carperitide for HF

Both before and after the clinical launch of carperitide in Japan, there has been no large-scale randomized double-blind study to confirm whether or not carperitide infusion improves cardiac function, clinical symptoms, and prognosis in patients with AHF or ADHF. However, two large-scale prospective open-label observational studies have been reported [41,42]. One observational study was conducted as a post-marketing surveillance study, in order to observe the efficacy and safety of carperitide. This study enrolled 3777 patients with AHF, who were administered carperitide at a median dosage of 0.085 \( \mu g/kg/min \) for a median duration of 65 h. During the infusion, 82% of the patients were clinically improved. The incidence of adverse events was 16.9%, most frequent being hypotension (9.5%), which occurred in the first 3 h of infusion, with 96% of patients recovering or improving without specific treatment [41]. Another observational study was Carperitide Effects Observed Through Monitoring Dyspnea in Acute Decompensated Heart Failure Study (COMPASS) [42]. COMPASS was conducted to evaluate the efficacy and safety of carperitide monotherapy in patients with AHF or ADHF; 1832 patients were enrolled. Prior to or in addition to carperitide \( P \) infusion, bolus injection of diuretic, nitrates, and digoxin was permitted. Carperitide was administered at an initial dose of less than 0.05 \( \mu g/kg/min \) in 82.2% of patients, and mean duration of the infusion was 5.2 ± 4.8 days. Improvement of subjective symptoms was evaluated by modified Borg scale; symptoms significantly declined within 2 h after the infusion. In 1524 patients (83.2%), carperitide infusion was stopped because of HF-related symptoms and signs, and was successfully replaced with standard oral agents for chronic HF. Adverse effects were observed in only 4.64% of the patients; the most frequently reported was hypotension, in 3.55%. Looking beyond the acute effect of carperitide on relief of symptoms, another study, PROTECT, investigated the effect of carperitide on the long-term prognosis of AHF [43]. The PROTECT study enrolled 49 patients with anterior ADHF who were randomly assigned into a group receiving low-dose carperitide (0.01–0.05 \( \mu g/kg/min \)) for 72 h and a group that received standard medical treatment. During the infusion, the cardiac free fatty acid-binding protein/serum creatinine ratio was reduced, suggesting inhibition of myocardial cell membrane damage. There was no significant difference in serum troponin \( T \) and creatinine levels between the two groups of patients. During an 18-month follow-up, incidence of death and rehospitalization was significantly lower in the carperitide group than in the control group. Thus, acute-phase transient low-dose ANP infusion improves the long-term prognosis in patients with ADHF. Although the mechanism for long-term beneficial effect of ANP is not clear at present, inhibition of the renin-angiotensin-aldosterone system [44] and/or anti-oxidant [45] effect of low-dose of ANP infusion may be involved in the mechanism.

Therapeutic use of ANP for AMI

Given that GC-A mice with permanent coronary artery ligation showed worse ventricular remodeling and prognosis than WT mice [29], ANP infusion has been hypothesized to improve prognosis in patients with AMI. Hayashi et al. [46] enrolled 60 patients with AMI who underwent emergent coronary intervention. After successful recanalization, 30 patients were randomly assigned into the ANP group (0.025 \( \mu g/kg/min \) of carperitide) and 30 patients into the nitroglycerin group 0.4 \( \mu g/kg/min \). Carperitide or nitroglycerin treatment lasted for more than 24 h, and was then replaced with oral inhibitors of the renin-angiotensin-aldosterone system in both groups of patients. At the end of the infusion, plasma angiotensin II, aldosterone, and endothelin levels were lower in the ANP group. Although the baseline hemodynamics and left ventricular function were similar in both groups, 1 month after onset the left ventricular end-diastolic volume index was significantly lower, and ejection fraction was significantly higher in the ANP group than the control group, indicating that ANP infusion improves left ventricular remodeling after AMI. To confirm this scenario in a larger population, Kitakaze et al. [47] conducted the J-WIND study, which is a multicenter prospective randomized single-blind study to evaluate efficacy of ANP infusion in the acute phase in patients with AMI, who received percutaneous coronary intervention. In the J-WIND study, 277 patients were assigned to the ANP group who received low-dose carperitide (0.025 \( \mu g/kg/min \)) for 72 h, and 292 to the control group, who received the same dose of vehicle. The primary endpoints were the infarct size, assessed as the area under the concentration versus time curve for creatine kinase; and ejection fraction in the chronic phase (6–12 months after the onset), assessed by left ventriculography. Infarct size was significantly decreased by ~15% in the ANP group (\( p < 0.016 \)), and ejection fraction was significantly higher (\( p < 0.024 \)). Incidence of cardiac death and HF, taken as secondary endpoints, was significantly lower in the ANP group. These studies indicate that ANP treatment is an effective adjunctive therapy in patients with AMI (Fig. 3).

Therapeutic application of ANP in renal diseases

Effect of ANP in renal function during cardiac surgery

More than 25 years have passed since the discovery of ANP, but there have been no case reports of ANP deficiency. However, during cardiopulmonary bypass in cardiac
surgery, the plasma ANP level decreased to an undetectable level. Because ANP and BNP are solely secreted from the heart, cardiopulmonary bypass artificially creates ANP and BNP deficiency. Sezai et al. [48] investigated the effect on renal function of ANP replacement therapy during cardiopulmonary bypass in 40 patients with normal renal function who underwent coronary-aorta bypass surgery. The 40 patients were randomly distributed between the ANP group and the control group. In the ANP group, carperitide infusion was begun just after cardiopulmonary bypass at a rate of 0.025 μg/kg/min for 24 h, and GFR was calculated by the serum creatinine level and urinary excretion of creatinine for 3 days. After cardiopulmonary bypass, GFR rapidly decreased to ∼70% level of the pre-operative level in the control group, but in the ANP group, GFR did not decrease and was maintained at a high level throughout the 3-day observation period, with concomitant favorable effects including larger urine volume, larger urinary excretion of sodium, and lower plasma aldosterone level compared with the control group.

**Protective effect of ANP on contrast-induced nephropathy**

Recently, renal-protective effect of ANP infusion was also demonstrated in patients who underwent cardiac catheterization. Contrast-induced nephropathy is one of the most important clinical complications associated with coronary angiography and enhancement of computed tomography. Recently, Morikawa et al. [49] reported prevention of contrast-induced nephropathy by ANP infusion. They conducted a prospective, randomized controlled trial in 254 consecutive patients with serum creatinine concentration higher than 1.3 mg/dl: 126 patients were treated with 0.042 μg/kg/min of carperitide plus 1.3 ml/kg/h of Ringer solution (ANP group), and 128 patients were treated with Ringer solution alone (control group). Either treatment was begun 4—6 h prior to the catheterization and lasted for 48 h. At baseline, there was no significant difference between the two groups in demographics including age, sex, blood pressure, renal function, ejection fraction, and frequency of drugs used. The prevalence of contrast-induced nephropathy, defined as a 25% increase or at least 0.5 mg/dl of increase in serum creatinine from baseline within 48 h, was significantly lower in the ANP group than in the control group (3.2% vs. 11.7%, p < 0.015). Serial changes in the serum creatinine level, serum cystatin C level and estimated GFR were compared between the two groups at 24 h, 48 h, 1 week, and 1 month after the procedures. These parameters for glomerular function slightly deteriorated in the control group but did not deteriorate in the ANP group; there was a significant difference in these parameters between the groups. However, biomarkers for tubular function, such as urinary β2-microglobulin and urinary N-acetyl-β-D-glucosamidase (NAG), were similar in both groups. The use of a volume of contrast medium >155 ml (odds ratio: 6.89; p < 0.001), and ANP treatment (odds ratio: 0.24; p < 0.016) were significant predictors of developing contrast-induced nephropathy (Fig. 4).

**Comparison between carperitide and nesiritide**

As mentioned above, because ANP and BNP bind the same receptor, GC-A, in order to stimulate biological effects, the main therapeutic uses of ANP and BNP are similar. However, BNP has a lower affinity for the clearance receptor and neutral endopeptidase, which degrades NPs and bradykinin, than ANP. Plasma half-lives of ANP and BNP

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Figure 3  Infarct size (A) and ejection fraction (B) as primary endpoints in the J-WIND trial. Reproduced from Kitakaze et al. [47] with permission.

Figure 4  Incidence of contrast-induced nephropathy (CIN). Reproduced from Morikawa et al. [49] with permission.
are $2.4 \pm 0.7$ and $12.1 \pm 3.0$ min, respectively, in patients with HF [50], which influence the dose of each peptide used. In the case of ANP treatment, usually it begins at a rate of $0.025–0.05 \mu \text{g/kg/min}$, whereas BNP treatment usually begins at a rate of $0.01 \mu \text{g/kg/min}$ following an initial $2 \mu \text{g/kg}$ of bolus injection. Furthermore, considering the difference in half-life of these peptides, it is reasonable to speculate that ANP more easily controls its effects and adverse effects, such as hypotension, than BNP.

In 2005, Sackner-Bernstein et al. reported that the intravenous administration of nesiritide might increase the serum creatinine level and the risk of short-term mortality (5). Although this report had a strong impact here in Japan, some cardiologists reacted with suspicion, because Japanese cardiologists felt that carperitide had a beneficial effect on renal function. A recent meta-analysis reported in 2009, showed that according to most of the trials presented, intravenous infusion of nesiritide in patients with ADHF neither worsens their renal function nor increases their short-term and long-term mortality (6). Furthermore, as mentioned above, carperitide may have a renal-protective effect.

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