Nesiritide in cardiovascular anesthesia
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Purpose of review
Acute heart failure has become a major medical issue in the western population. Because mortality is still as high as 50%, the treatment of these patients has been the focus of many studies. A new approach has recently been proposed, including B-type natriuretic peptide as a medication. The purpose of this review is to discuss these new developments.

Recent findings
Recent studies have shown that plasma levels of B-type natriuretic peptide may serve as a marker for the severity of acute decompensated heart failure. Nesiritide, which is the recombinant equivalent of B-type natriuretic peptide, is a vasodilator, acting by increasing cyclic guanosine 3',5'-monophosphate in the vascular smooth muscle cells. It is mainly considered to be an alternative for nitroglycerin, because it has fewer side-effects, and its activity is more prolonged. Treatment with nesiritide has shown fewer arrhythmias and a lower mortality rate compared with dobutamine and milrinone. In cardiac surgery, nesiritide is mainly administered to patients awaiting heart transplantation, but intraoperatively the doses of nesiritide and anesthetics must be adjusted because of a potential interaction. A few anecdotal reports have shown the advantageous effects of nesiritide in the early post-bypass period.

Summary
Anesthesiologists will be confronted with increasing numbers of patients with heart failure, who require new forms of medication. Nesiritide is a promising new tool, and its application, which is still mainly restricted to the preoperative period, will probably soon be extended to the early post-bypass period.

Keywords
anesthesia, cardiac surgery, heart failure, hemodynamics, renal function

Abbreviations
BNP  B-type natriuretic peptide
NPR  natriuretic peptide receptor
PCWP  pulmonary capillary wedge pressure
VAMC  Vasodilation in the Management of Acute Congestive Heart Failure (study)

Introduction
Heart failure has become a major problem in healthcare in the United States and Europe, affecting a total of almost a million individuals, and accounts for at least 5 million hospitalizations annually. The 5-year mortality rate is estimated at 45–50% [1**,2**].

The diagnosis of acute heart failure is often complicated by the presence of several co-morbidities, which makes the availability of a potential marker for the assessment of the severity of the disease an essential diagnostic tool.

B-type natriuretic peptide
Neurohormones such as natriuretic peptides have gained considerable popularity as diagnostic markers for congestive heart failure. Atrial natriuretic peptide was the first natriuretic peptide isolated from the atria and ventricles of decompensated hearts. Later followed the discovery of brain natriuretic peptide, initially identified in the porcine brain, and later isolated from the ventricles of the myocardium in response to ventricular dysfunction and wall stress. It was called B-type natriuretic peptide (BNP), and is as such more specific as a marker for acute heart failure than atrial natriuretic peptide [3**].

In a combined overview of multiple small studies, Maisel et al. [4**] concluded that a BNP plasma level of 100 pg/ml, measured by fluorescence immunoassay, had an accuracy of 83.4% to diagnose acute heart failure, and a level of 50 pg/ml had a negative predictive value of 96%, showing that a low BNP plasma level indicates the absence of acute heart failure. Elevated levels of BNP are not only present during primary acute heart failure, but may be related to secondary right heart failure in the case of pulmonary embolism, severe lung disease or an exacerbation of established systolic dysfunction resulting from other causes.

In a recent observational study, Charpentier et al. [5] reported that BNP plasma levels in septic patients were
related to the severity of myocardial dysfunction, and showed a prognostic value for mortality.

The biological activities of the natriuretic peptides are mediated by natriuretic peptide receptors (NPRs), of which three classes have been identified: NPR-A, NPR-B and NPR-C [6**]. BNP binds predominantly to NPR-A receptors, which are mainly present in large vessels, kidneys and adrenals. Binding of NPR-A receptors leads to the synthesis of cyclic guanosine 3', 5'-monophosphate, inducing vasodilatation [7].

The physiological effects of BNP also include inhibition of the production of angiotensin II, norepinephrine and endothelin. In addition, because of the hemodynamic and tubular effects, BNP has natriuretic and diuretic properties and diminishes myocardial fibrosis [6**].

**Nesiritide**

Because of the attractive physiological and biological properties of BNP, the recombinant human form of BNP, called nesiritide, was synthesized and recently introduced for the treatment of patients with decompensated heart failure.

**Pharmacokinetics**

Nesiritide is a 32 amino acid peptide (Fig. 1), similar to the naturally occurring BNP, and when administered intravenously it fits a two-compartment model with a rapid distribution half-life of 2 min and a mean terminal elimination half-life of 18 min. The mean volume of distribution is 0.19 l/kg [3**].

Nesiritide is cleared in three ways: direct binding to the NPR-C surface receptor, which is internalized, leading to the degradation of nesiritide by proteolytic enzymes in lysosomes; proteolytic cleavage on the surface of the vascular endothelium; and renal filtration. Renal filtration is the least important mechanism. The mean clearance of nesiritide is 9.2 ml/min/kg.

**Pharmacodynamics**

The hemodynamic effects of nesiritide, mainly consisting of the lowering of pulmonary capillary wedge pressure (PCWP) and systolic blood pressure, are observed in the first 15 min of an infusion, with maximal effects occurring within 1–3 h [6**].

**Heart failure**

It is not surprising that the first controlled clinical studies with nesiritide included patients with compensated heart failure. They showed a hormonal balance tilted towards vasoconstriction, water and salt retention, as a result of increased plasma levels of aldosterone, endothelin, vasopressin and catecholamines [7].

These preliminary studies focused mainly on the hemodynamic effects of nesiritide, showing that it produces dose-dependent arterial and venous vasodilatation. This effect appeared to be mediated, similar to natural BNP, by the activation of cyclic guanosine 3', 5'-monophosphate-coupled receptor NPR-A, which is present in the endothelium. It showed no inotropic properties and caused no reflex tachycardia. Cardiac output increased, mainly as a result of an increase in stroke volume [3**].

One of the interesting findings in these first studies included the decrease in plasma aldosterone levels without an effect on renin levels. This suggests a direct inhibitory effect on the adrenal glands [6**]. In addition, during nesiritide infusion plasma endothelin levels also decreased, combined with an increase in urine output and sodium excretion [8].

The routine treatment of patients with decompensated heart failure includes the intravenous administration of dobutamine, nitroglycerine, and furosemide. Milrinone, a phosphodiesterase inhibitor, was recently successfully introduced as an alternative inotropic and vasodilating agent [2**].

All the intravenous inotropes and vasodilating compounds have more or less serious side-effects, as listed in Table 1 and Table 2. They consist mainly of tachycardia, hypotension and arrhythmias. As none of these phenomena were detected during the first clinical efficacy studies with nesiritide [9], comparative trials between nesiritide and dobutamine, and nesiritide and nitroglycerin were designed.

In patients with acutely decompensated congestive heart failure, nesiritide produced fewer ventricular

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**Figure 1. The amino acid sequence of nesiritide (recombinant human B-type natriuretic peptide)**

rhBNP, recombinant human B-type natriuretic peptide.
arrhythmias, including cardiac arrest, compared with dobutamine [10]. The mortality rate tended to be lower with nesiritide, although it did not reach statistical significance in one of the two studies [11].

In a larger multicenter, prospective, placebo-controlled trial, called the Vasodilation in the Management of Acute Congestive Heart Failure (VAMC) study [12], nesiritide was compared with nitroglycerin in patients with dyspnea at rest from decompensated congestive heart failure. The results showed a significantly greater reduction in PCWP with nesiritide, combined with a more pronounced early increase in cardiac output. After 3 h of treatment no significant differences were detected between the study groups, although the hemodynamic effects of nitroglycerin were significantly less pronounced than those observed with nesiritide during the first 24 h. Symptoms such as headache and abdominal pain were reported significantly more often in the nitroglycerin group. The most important side-effect in the nesiritide-treated patients consisted of mild hypotension, whereas headache was significantly more often observed in the nitroglycerin-treated patients. Although nitroglycerin is an effective vasodilator in acute heart failure, its use is limited by tachyphylaxis and underdosing. An important finding was the absence of the development of ventricular arrhythmias, which is a well documented life-threatening side-effect of inotropic agents such as dobutamine and milrinone [13**]. In a retrospective study [14*], nesiritide was shown to have a greater improvement on hemodynamics, a shorter length of intensive care unit stay, and an overall reduction in hospital costs when compared with milrinone in patients with acutely decompensated heart failure. The lower incidence of arrhythmias with nesiritide compared with other treatment strategies is probably caused by the improved balance between oxygen supply and demand, as was reported in a group of non-heart failure patients [15]. Nesiritide decreased left ventricular filling pressures, increased coronary artery blood flow, and decreased coronary artery resistance, whereas myocardial oxygen uptake decreased.

Patients with heart failure who develop renal insufficiency have a relatively poor prognosis. It is well established that these patients have a high prevalence of coronary artery disease, which makes them unsuitable for treatment with inotropic agents such as dopamine and dobutamine. From the VAMC database, Butler et al. [16*] evaluated the efficacy and safety of nesiritide in a group of patients with moderate and advanced renal insufficiency, compared with a group without renal insufficiency. Nesiritide reduced PCWP better and relieved the symptoms of dyspnea more robustly at any timepoint than nitroglycerin, without causing a change in renal function.

In another subset of patients in the VAMC, nesiritide appeared to be effective in reducing PCWP, diminishing dyspnea, and preventing readmission in patients with acute coronary syndromes [17]. These results were mostly better than in the nitroglycerin group.

Apart from its effects on left ventricular dynamics, it is to be expected that nesiritide, like nitroglycerin, has the capability of lowering pulmonary artery pressure, and

### Table 1. Inotropic agents for the treatment of acute heart failure

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>HR</th>
<th>MAP</th>
<th>PCWP</th>
<th>CO</th>
<th>SVR</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>2.5–10 μg/kg/min</td>
<td>0/1</td>
<td>0/1</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Arhythmias, angina, palpitations, hypokalemia</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.5–3 μg/kg/min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/1</td>
<td>↓</td>
<td>Arhythmias, hypertension, angina, decreased peripheral perfusion</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.03–0.15 μg/kg/min</td>
<td>↑↑</td>
<td>↑</td>
<td>0</td>
<td>↑</td>
<td>↓</td>
<td>Arhythmias, hypokalemia, lactic acidosis</td>
</tr>
<tr>
<td>Milrinone</td>
<td>loading 24 μg/kg</td>
<td>0/1</td>
<td>0/1</td>
<td>↓</td>
<td>0/1</td>
<td>↓</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>0.1–0.2 μg/kg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

### Table 2. Vasodilating agents for the treatment of acute heart failure

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>HR</th>
<th>MAP</th>
<th>PCWP</th>
<th>CO</th>
<th>SVR</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>0.3–2.5 μg/kg/min</td>
<td>0/1</td>
<td>0/1</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Headache, dizziness, reflex tachycardia, hypotension</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.3–2.5 μg/kg/min</td>
<td>0/1</td>
<td>0/1</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>= Nitroglycerin, thiocyanate toxicity</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20–40 mg/h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Hypokalemia, hypocalcemia, hypomagnesemia, orthostatic hypotension</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>2 μg/kg bolus, 0.01–0.03 μg/kg/min</td>
<td>0</td>
<td></td>
<td>0/1</td>
<td></td>
<td></td>
<td>Symptomatic and asymptomatic hypotension</td>
</tr>
</tbody>
</table>

CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.
reducing right ventricular afterload [18]. In a recent case report [19], nesiritide decreased pulmonary vascular resistance in a patient with rheumatic mitral valve disease and pulmonary hypertension, which was refractory to traditional therapy, including prostacyclin. An important additional finding was the improvement in renal function.

**Cardiovascular surgery and anesthesia**

It is to be expected that BNP and nesiritide will play an important role in the management of the cardiac surgery patient. The first indication of this application was the study by Hufleq et al. [20**], which showed that a preoperative BNP plasma level greater than 385 pg/ml predicts postoperative complications and one-year mortality after cardiac surgery. Elevated postoperative BNP plasma levels were associated with prolonged hospital stay and mortality within one year. In the near future, BNP plasma levels may be one of the factors for determining the right timing of surgery. As the anesthesiologist will be confronted with a still growing surgical population with some form of heart failure [21**], BNP plasma levels could be one of the decisive factors in the preoperative assessment of patients.

No studies have been published on the use of nesiritide during cardiovascular anesthesia, but there is already some experience with the management of patients on preoperative nesiritide therapy. Most of these patients are awaiting heart transplantation, and are treated with inotropes and nesiritide [22,23].

In pediatrics, the limited experience with the administration of nesiritide in patients awaiting heart transplantation has shown a significant improvement in urine output without any hypotensive complications [24]. It is still too early to transfer the adult data to these patients, because congenital heart disease often leads to failure because of high output in the presence of preserved myocardial function [25**].

The challenge for the anesthesiologist is to manage these unstable cardiac transplant patients safely until the institution of cardiopulmonary bypass, particularly when they have previously undergone multiple cardiac surgery procedures. At Stanford, in-hospital transplant recipients are routinely treated with a combination of dobutamine, dopamine and nesiritide, often supported by a left-ventricular assist device. As many anesthetic agents have the tendency to lower blood pressure, it is routine to diminish the nesiritide dose temporarily by 50% during and immediately after the induction of anesthesia, and to adjust the dose afterwards according to the hemodynamic profile of the patient. Although nesiritide has a longer half-life than nitroglycerin, it is surprising to observe the immediate hemodynamic changes, similar to the experience with nitroglycerin, during the adjustment of the dose.

There is still little experience with the use of nesiritide in the early postoperative period after cardiac surgery. The most recent reports include patients who postoperatively showed symptoms of heart failure 48 h after mitral valve surgery or heart transplantation [26,27]. In both reports, nesiritide effectively improved hemodynamics, including an increase in diuresis. In another case report [28], nesiritide was administered to two patients who developed heart failure after coronary artery bypass surgery. In both patients, right and left-sided filling pressures decreased, and urine output significantly increased, without any change in serum creatinine or sodium levels.

Cardiac anesthesiologists are used to managing cardiac surgical patients in the early post-bypass period. The varying degrees of ischemia, combined with residual myocardial dysfunction after correction, typically cause diastolic dysfunction in the presence of elevated levels of catecholamines, aldosterone, and endothelin. In addition, the early postoperative hemodynamic profile of the patient undergoing heart transplantation is often characterized by right ventricular dysfunction in the presence of pulmonary hypertension [29**]. Because of its attractive pharmacological profile, and referring to the experiences in patients with acute heart failure, nesiritide could become one of the agents of choice in the management of these patients.

**Conclusion**

From the anesthesiologist’s point of view it is important to pay attention to developments in the medical treatment of patients with acute heart failure, because increasingly greater numbers of these patients will be presented as surgical candidates. Nesiritide has the potential to become a drug of choice in this respect, and is already administered preoperatively to transplant candidates, urging the anesthesiologist to adjust anesthetic management during the pre-bypass period. It is to be expected that nesiritide will also be administered in the early post-bypass period to manage diastolic dysfunction and pulmonary hypertension.

Multicenter trials will have to show that short and long-term outcomes improve when nesiritide is administered early in the course of treatment instead of late, as is the case at present. Analysis of the cost-effectiveness should play an important role, although the often complex clinical settings may not allow for a clear result in this respect.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


An editorial with useful statistics.

An excellent review of the current treatment of heart failure, including the description of all new pharmacological agents.


The first study on the difference in arrhythmogenicity between milrinone and nesiritide.


A review of the molecular biology of BNP and nesiritide, including recommendations and therapeutic considerations.


The best overview of the diagnostic properties of BNP, including considerations on secondary heart failure.


The most recent, extensive review on the role of BNP in the diagnosis of heart failure, with up-to-date algorithms and time tables.


An excellent review of future developments, indicating the growing surgical population with various degrees of heart failure.


This study shows the unique renal pro-


This study shows the unique renal profile of nesiritide in a subset of patients from the VMAC database.


This study clearly shows the importance of BNP as a marker for surgical outcome, and its potential role in the management of cardiac surgical patients.


An excellent review of many clinical issues concerning the modern aspects of heart failure.