

Neuroendocrine activation after myocardial infarction: causes and consequences

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Increases in plasma concentrations of a number of neuroendocrine substances are well documented after myocardial infarction. The objectives of this paper are to describe the time course of neuroendocrine activation after myocardial infarction, the evidence for activation of the cardiac renin-angiotensin system, possible causes and consequences of neuroendocrine activation, the influence of patient genotype on outcome, and the ability of early neuroendocrine activation to predict prognosis.

The time course of neuroendocrine activation

Plasma concentrations of renin, angiotensin II, and aldosterone are generally increased by the time patients suffering from myocardial infarction are admitted to the hospital.¹⁻⁴ In patients with uncomplicated myocardial infarction, studies have suggested that plasma concentrations of renin, angiotensin II, and aldosterone rise only slightly before returning to normal levels during the first three days following infarction. However, in patients developing heart failure requiring diuretics, activation is exaggerated and sustained.¹⁻³ Patients who have sustained large infarcts but who have not required diuretic therapy also have increased renin-angiotensin-aldosterone system (RAAS) activity up to two weeks after infarction,^{5,6} but probably not in the long term.⁷⁻¹⁰ Plasma angiotensin converting enzyme (ACE) activity does not change,² suggesting that activation of renin rather than ACE is responsible for the rise in angiotensin II after infarction. The possibility that tissue RAAS is activated after myocardial infarction is discussed in more detail below.

Plasma concentrations of noradrenaline and adrenaline are also raised early after infarction and decline progressively thereafter.^{1,3} Mean levels are still slightly above those of control groups at discharge in patients with uncomplicated myocardial infarction.¹ Regardless of diuretic treatment, patients sustaining large infarctions have raised noradrenaline levels that can remain high 14 days after infarction.^{5,6} In contrast to plasma renin, plasma concentra-

tions of noradrenaline remain elevated in patients with chronic asymptomatic left ventricular dysfunction¹⁰ or untreated heart failure.⁷⁻⁹ Plasma concentrations of neuropeptide Y, a substance co-secreted with noradrenaline from sympathetic nerve terminals, are also markedly raised initially. Neuropeptide Y concentrations peak approximately eight hours after myocardial infarction and return to the normal range within two to three days unless heart failure supervenes, in which case they may become chronically elevated in patients suffering from heart failure.^{11,12} Cardiac sympathetic activity, measured by noradrenaline spillover, is also increased in unstable angina.¹³

Plasma concentrations of antidiuretic hormone (ADH) are markedly raised early after infarction but decline rapidly.^{1,14} ADH is raised in patients with chronic asymptomatic left ventricular dysfunction, suggesting that the hormone is chronically activated after large infarctions.¹⁰

Plasma concentrations of endothelin are also raised in patients suffering from myocardial infarction.^{15,16} The values are elevated immediately after infarction and tend to increase further in the ensuing hours, before subsiding to normal levels over the following weeks, unless complications occur.¹⁷⁻¹⁹

Patients suffering from myocardial infarction have raised plasma concentrations of atrial natriuretic factor (ANF) upon admission to the hospital. The values commonly fall within the first few hours after admission,²⁰⁻²² but rise back to admission levels and remain elevated thereafter.^{2,14,23} In patients with small infarcts, ANF concentrations may return to the upper limit of the normal range over the following two weeks. Plasma ANF remains distinctly elevated in patients sustaining large infarctions even during long term follow up,^{2,10} regardless of the development of heart failure.

The pattern of activation of brain natriuretic peptide (BNP) after myocardial infarction appears different from that of ANF; plasma concentrations climb steadily over the first 24 hours.²¹ In patients with smaller infarcts, plasma BNP declines after the first 24 hours but does not reach normal levels until at least four weeks after the infarction. In patients with larger infarcts there appears to be a secondary peak in BNP around the fifth day and plasma BNP remains elevated long term.^{21,24}

N-terminal ANF (NT-ANF) is also raised during myocardial infarction. Plasma concentrations of NT-ANF reach a peak four days after infarction and return to the normal range (in uncomplicated cases) within two weeks.²⁵

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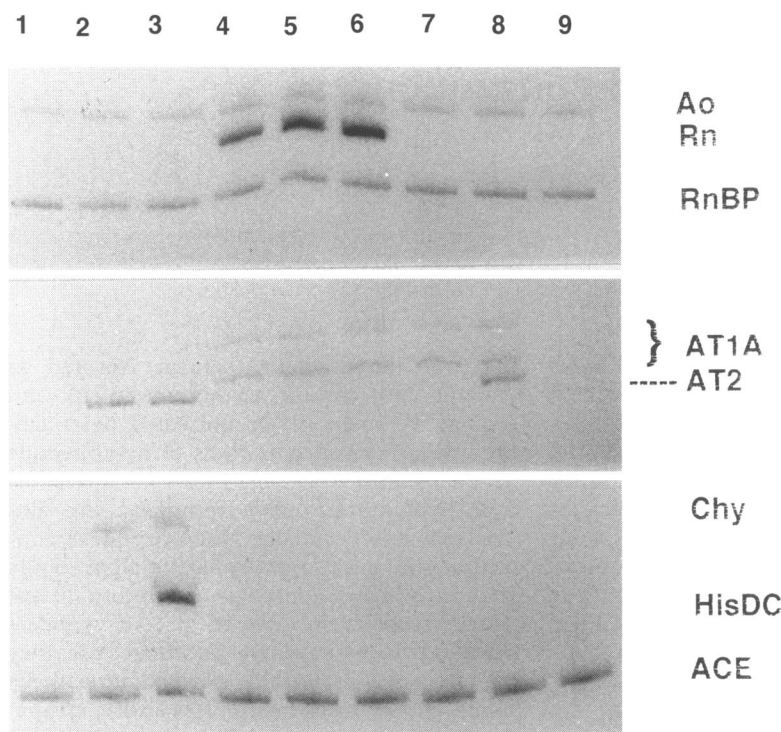
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Glossary of trials

CONSENSUS II—Cooperative New Scandinavian Enalapril Survival Study II

SAVE—Survival and Ventricular Enlargement Study



Qualitative analysis of gene coexpression in human cells in primary culture. Lanes 1–3: lymphoblastoid cells, 4–6: skin fibroblasts, 7: cardiac fibroblasts, 8: tricuspid valve fibroblasts, 9: arterial endothelial cells. Radiolabelled fragments of DNA were generated by reverse transcription-polymerase chain reaction (RT-PCR) amplification of total cellular RNA purified from the different cell types and then loaded onto a 6% polyacrylamide gel for electrophoresis and autoradiography. Primers specific for angiotensinogen (Ao), renin (Rn), renin binding protein (RnBP), and angiotensin-I converting enzyme (ACE) were used in separate analyses and the identity of all products was confirmed by direct dideoxy cycle sequencing.

In contrast to C-terminal ANF (CT-ANF), NT-ANF does not appear to show an early decline.²⁶ In patients with chronic asymptomatic left ventricular dysfunction NT-ANF remains elevated.^{27 28}

ACTIVATION OF THE CARDIAC RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN MYOCARDIAL INFARCTION

The primary stimuli inducing tissue RAAS activation are obscure. Massive changes in the activity of the plasma RAAS caused by hypoperfusion of key organs (lung, kidney, and liver) may perturb the local intracardiac system. Alternatively, increases in the levels of numerous growth factors and distress molecules within damaged tissue may alter angiotensin turnover.

The rat infarct model shows that homeostatic regulation of the intracardiac RAAS is significantly disturbed following myocardial infarction. Angiotensin binding is dramatically increased at the site of infarction,²⁹ and ACE production is induced in endothelial cells within the vicinity of the tissue damage.³⁰ Localised activation of angiotensinogen production probably occurs, but it is still unclear whether renin production is induced locally.

A variety of cell types responds to trauma and contributes to a dynamic cardiac repair process. Endothelial cells and vascular smooth muscle cells are activated and begin to proliferate. Fibroblasts, tissue mast cells, and macrophages are also activated. Cellular debris is processed within granulation tissue, and scar tissue is generated and revascularised. Rapid

changes in the levels of angiotensin peptides at the site of infarction may exert complex effects on RAAS component production in the surrounding tissue.³¹ Mechanical stress on the surviving myocardium may exert a global effect on stretch regulated genes³² depending on the size of the infarct.

The losartan sensitive angiotensin II type 1 receptor (AT-1) subtype is specifically induced in rat infarct scar tissue at an early stage after infarction, but identifying the cell types expressing increased levels of receptor is difficult. Receptor localisation has been correlated with production of markers of tissue repair such as collagen, but further studies at the cellular, protein, and gene expression levels are required to increase our understanding of the rat infarct model.^{33 34}

STUDIES OF HUMAN TISSUE

Analysing human cardiac tissue is more difficult than studying a whole rat heart or its individual chambers. Technical problems exist with respect to the physical size of the human heart and selection of appropriate tissue samples for analysis. As indicated above, activation of the myocardial RAAS may be associated with granulation tissue, inflammation, aging scar tissue, and mechanical stretch in different regions of the same chamber. Old scar tissue might be biochemically distinct from recently repaired sites of necrosis. Important mechanistic clues concerning the function of the human cardiac RAAS post-infarction are therefore likely to be unravelled by cell culture studies capable of mimicking different physiological conditions.^{35 36} Some human cells can express all components of the RAAS (figure), suggesting the existence of an autocrine system. Other cell types can express only a limited number of components, indicative of their involvement in a system subject to paracrine regulation.

Causes of plasma neuroendocrine activation after myocardial infarction

Myocardial infarction is painful, provokes intense anxiety, and is often associated with tachycardia and sometimes hypoxia. It may cause a fall in cardiac output and renal perfusion which leads to activation of arterial baroreflexes. In addition, myocardial infarction causes a rise in left ventricular diastolic pressure and therefore atrial pressures, and is treated with a cocktail of agents. All of these effects are likely to alter neuroendocrine function. In addition, as the heart is itself a neuroendocrine organ, local damage may alter its secretory function.

PAIN, ANXIETY, AND OPIATES

Pain and anxiety are potent stimuli to sympathetic activation. Relief of pain is likely to be an important factor in reducing early sympathetic activation, but opiates are a powerful stimulus to ADH release.¹

NEUROENDOCRINE CONSEQUENCES OF SYMPATHETIC ACTIVATION

Sympathetic activation stimulates renal renin release; therefore plasma renin correlates with

plasma noradrenaline.^{1,37} Tachycardia resulting from increased sympathetic activity could also lead to an increase in ANF.

ARTERIAL BAROREFLEX ACTIVATION

A decrease in arterial pressure leads to baroreflex activation and an increase in sympathetic activation. Head-up tilt activates arterial baroreflexes and increases plasma noradrenaline. The rise in plasma noradrenaline with head-up tilt appears to be increased late (one month) after myocardial infarction. This is associated with an exaggerated increase in angiotensin II.² This is somewhat surprising and awaits confirmation, as arterial baroreflexes have been reported to be blunted after myocardial infarction and in heart failure.

Exercise also increases plasma ANF, renin, and noradrenaline. The increase in ANF levels during exercise appears exaggerated in patients two to three weeks after infarction. The increases in renin and noradrenaline are not significantly different from those found in healthy controls.³⁸

Renal vasoconstriction

Renal vasoconstriction is well documented after infarction and initially reflects sympathetic activation.³⁹ Once renal vasoconstriction has occurred this stimulates secretion of renin. The resulting increase in angiotensin II causes further renal vasoconstriction.

Increased ventricular filling/atrial pressure

Due to the loss of forward stroke volume and a decline in the compliance of infarcted and ischaemic myocardium, ventricular filling and atrial pressure rise. A rise in right and left filling pressures is likely to be a major determinant of ANF secretion,^{40,41} possibly especially right ventricular filling. Some investigators have noted an early decline in plasma concentrations of ANF following myocardial infarction.^{2,14,20,21,23} There are several possible explanations for this phenomenon. One theory suggests that early secretion depletes the stored supply of pre-existing ANF. Increases in plasma ANF concentrations that are observed several hours after myocardial infarction are due to synthesis of new ANF stimulated by a rise in ventricular filling pressure. Another theory suggests that early cardiac dilatation is limited by pericardial constraint; as ANF secretion reflects the transmural pressure gradient rather than the intracardiac pressure, this could be an important modulating effect. Alternatively, administration of vasodilator agents such as nitrates, ACE inhibitors, and streptokinase, may off-load the ventricle and lead to a transient dip in the stimulus to ANF secretion. None of these explanations is entirely satisfactory as the changes in ANF do not seem to be closely accompanied by changes in BNP or NT-ANF.^{21,25}

Increases in right atrial pressure should attenuate the increase in ADH and renin that is seen in patients suffering from myocardial

infarction, mediated vagally through low pressure baroreceptors or through ANF and BNP.^{42,43} If marked increases in venous pressure occur, the resulting hepatic congestion will impair aldosterone catabolism, leading to a rise in plasma aldosterone.

Hypoxia

This is a not uncommon finding after myocardial infarction. It probably reflects both opiate-induced hypoventilation and a fall in pulmonary diffusion capacity.⁴⁴ Hypoxia is a powerful stimulus to sympathetic activation.

Effects of treatment

THROMBOLYSIS

Streptokinase is a powerful vasodilator²⁰ which activates arterial baroreflexes, leading to an increase in plasma renin, angiotensin II, and catecholamines.²⁰ Tissue plasminogen activator is not associated with vasodilation or hypotension or further activation of the RAS.⁴ The administration of an ACE inhibitor within a few hours of streptokinase is likely to aggravate hypotension. This may be one reason why the administration of ACE inhibitors shortly after myocardial infarction may be less effective in reducing mortality.⁴⁵ The effects of thrombolysis on ANF are controversial, but streptokinase probably reduces ANF as discussed above.^{2,20,22} In the long term, thrombolysis, by reducing ventricular damage, should reduce neuroendocrine activation.²²

NITRATES

Nitrates reduce filling pressures and arterial pressure and therefore ANF. Cautious use of nitrates may not increase renin or sympathetic activity; however, increases may occur when hypotensive doses are given.⁴²

DIURETICS

Diuretics reduce ventricular filling pressures and circulating volume. Consequently, diuretics reduce ANF and activate the renin-angiotensin and the sympathetic nervous system.^{42,46}

ASPIRIN

Although early aspirin treatment has a clearly beneficial effect after myocardial infarction, the possibility that long term aspirin may be harmful in patients who subsequently develop heart failure has been raised.⁴⁷ This may be due to inhibition of vasodilator prostaglandin synthesis.

β BLOCKERS

Cross sectional studies suggest that patients treated with β blockers have lowered plasma renin activity but that resting ANF and noradrenaline values are similar to those in non-treated patients.^{38,48} During exercise, patients treated with β blockers have suppressed renin, increased plasma concentrations of ANF, and unchanged plasma noradrenaline.

CALCIUM ANTAGONISTS

There is little post-infarction data on the use of calcium antagonists. In heart failure, calcium

antagonists generally increase renin-angiotensin and sympathetic nervous system activity.⁴² It is unclear whether newer dihydropyridine calcium antagonists have a similar effect on these systems.

ACE INHIBITORS

ACE inhibitors inhibit the production of angiotensin II⁴⁹ and reduce plasma concentrations of aldosterone and noradrenaline⁴⁹ in the early hours after infarction. In patients who have sustained large infarcts, ACE inhibitors suppress the sustained increase in angiotensin II and aldosterone.⁵⁰ However, in patients with uncomplicated infarcts, it is difficult to determine the continuing effect of ACE inhibitors because neuroendocrine variables decline naturally in the days following myocardial infarction.^{23 51} The natriuretic peptides are markers of ventricular dysfunction and, as ACE inhibitors have beneficial effects on remodelling, it is not surprising that some studies^{24 51 52} suggest that ACE inhibitors reduce levels of natriuretic peptides, though there are exceptions.⁵⁰ There is no rebound increase in NT-ANF after withdrawal from six months of treatment with enalapril.⁵²

Effects of genotype

The DD polymorphism of the ACE gene is associated with higher circulating levels of ACE which could influence post-infarction remodelling. The DD genotype is associated with a greater increase in plasma noradrenaline in the early hours of infarction and a more marked degree of long term cardiac dilatation.⁵³ The ACE inhibitor captopril prevented these effects of the DD genotype, suggesting that the increase in plasma ACE associated with the DD genotype is of functional significance.⁵³

Consequences of neuroendocrine activation after myocardial infarction

These have been discussed in more detail in a previous supplement to the *British Heart Journal*.⁵⁴

VENTRICULAR REMODELLING

Activation of neuroendocrine systems has been held responsible for adverse ventricular remodelling after myocardial infarction. Patients with large infarcts are more likely to have progressive ventricular dilatation, develop heart failure, and die. These patients are also more likely to have activation of neuroendocrine systems and therefore an association between activation and remodelling seems inevitable.

Increases in angiotensin II have a positive inotropic effect, can cause cardiac myocyte necrosis with replacement fibrosis and cardiac myocyte hypertrophy, and can stimulate fibroblast proliferation and collagen synthesis. Aldosterone may also have an independent effect on collagen deposition. The RAAS may play an important role in the maturation of the infarct scar with a potentially favourable effect. Increases in catecholamines may also cause cardiac myocyte necrosis. It is not clear if the natriuretic peptides have an important effect on cardiac remodelling.

Although ACE inhibitors exert a favourable effect on ventricular remodelling, it is not certain whether this reflects solely their effect on haemodynamics or also a more direct action on the myocardium.

Vascular effects

Increases in angiotensin II, sympathetic activity, and ADH cause arterial constriction, which increases the afterload on the damaged heart. Increases in afterload may result in an increase in preload, as the damaged ventricle fails to discharge its contents adequately. This leads to ventricular dilatation. Local arteriolar constriction at the site of infarction may also be beneficial, by helping to prevent haemorrhage into the infarct. Sympathetic activation has powerful vasoconstrictor effects that may be enhanced by angiotensin II and ADH. This results in an exacerbation of the rise in preload. ANF and BNP, as well as increases in vasodilator prostaglandins and nitric oxide, limit vasoconstriction but are overwhelmed when heart failure occurs. Vasoconstriction may be superseded by structural changes in vascular architecture in the systemic and pulmonary circulations that may be difficult or impossible to reverse. It is likely that neuroendocrine activation plays an important role in the transition from functional to structural increases in vascular resistance.

Renal effects

The cause of salt and water retention in human heart failure is unknown. Animal experiments suggest that the RAAS or sympathetic nervous system may be critical to the development of renal sodium and water retention. Aldosterone antagonists, ACE inhibitors, or drugs that interfere with the sympathetic nervous system do not prevent salt and water retention in heart failure. Only one study of ACE inhibitors in heart failure has noted a reduction in body weight compared to placebo.⁵⁵ Although ACE inhibitors improve renal blood flow in myocardial infarction³⁹ and in heart failure,^{43 46} they impair glomerular filtration.

Effects on arrhythmias

The effect of angiotensin II on arrhythmias remains controversial, although most post-infarction studies have shown that ACE inhibitors reduce ventricular arrhythmias.^{49 56} There is considerable evidence that sympathetic activation is arrhythmogenic. Activation of both the RAAS and the sympathetic nervous system is capable of producing hypokalaemia and inhibition of aldosterone formation, or the β_2 receptor may be beneficial in this respect.

Neuroendocrine activation and prognosis

Data from the SAVE and CONSENSUS II studies and a series of smaller studies have related neuroendocrine variables to prognosis after infarction.^{11 28 57 62} These data could be used in at least three ways. First, neuroen-

Table 1 Relation between neuroendocrine activation and prognosis after myocardial infarction

Author/year	n	Excluded therapies at sampling stratification	Sampling day	Follow up	Variables	Prognostic significance	
						Univariate	Multivariate
Svanegaard/92 ⁵⁷	55	No "vaso active" drugs <200 pg/ml>	Admission	36	ANF	P = 0.006	NS
Omland/93 ^{*60}	145	<median>	Day 3	12	Killip class	P = 0.014	NS
Omland/93 ^{*61}	139	<Varied>	Day 3	12	ANF	P < 0.001	P < 0.05
Omland/94 ^{*59}	142	<75th Centile>	Day 3	12	Noradrenaline	P = 0.009	NS
Omland/95 ^{*58}	145	<Median>	Day 3	43	Adrenaline	P = 0.048	NS
Echo SS	85				NT-ANF	P = 0.0003	P = 0.003
					ANF	P = 0.0004	NS
					Killip class	P = 0.001	NS
					Endothelin	P < 0.0001	P < 0.0001
					ANF	P = 0.013	NS
					Killip class	P = 0.0025	
					ANF	P < 0.0001	NS
					Endothelin	P < 0.001	NS
					Noradrenaline	P = 0.0335	NS
					Killip class	P < 0.0001	P = 0.02
					LVEF	P < 0.001	P < 0.01
					Renin	P < 0.001	P = 0.05
					Aldosterone	P < 0.001	NS
					Noradrenaline	P = 0.024	NS
					Adrenaline	NS	NS
					Dopamine	NS	NS
					ANF	P < 0.001	P = 0.006
					ADH	P = 0.01	NS
					NT-ANF	P < 0.001	P = 0.012
Hall/94 ^{†28}	246	ACE Inhibitors <values in the top 2.5% of the normal population>	Day 12	32			
Ullman/94 ^{†11}	113	<60 pmol/l>	Admission	24	Neuropeptide Y	P = 0.07	NS
Arakawa/94 ^{‡3}	70	<59 pg/ml>	Admission	18	BNP	P < 0.01	P = 0.0001
Omland/94 ^{‡68}	131	<75th Centile>	Day 3	42	BNP	P < 0.0001	P < 0.001
					ANP	P < 0.0001	NS
					NT-ANP	P = 0.0002	NS

*Substudies of CONSENSUS II.

†Substudies of SAVE.

ANF, atrial natriuretic factor; NT, N-terminal; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

doctrines activation could be used to predict those with major ventricular dysfunction (for example, an ejection fraction of < 40%), a subgroup of patients at higher risk of death and in whom long term treatment with ACE inhibitors has been shown to improve prognosis. Second, neuroendocrine variables could themselves be used to identify patients at high risk in whom long term treatment might be appropriate. Third, it is possible that neuroendocrine variables have the ability to identify that subgroup of patients with left ventricular dysfunction who are at especially high risk.

The studies of neuroendocrine variables after infarction show that all are increased to a greater extent in patients with larger infarcts and, perhaps more importantly (as many patients will have more than one infarct), patients with the poorest residual ventricular function. As right and left ventricular infarction may have different effects on haemody-

namics and neuroendocrine activation, a strong relation between left ventricular function and neuroendocrine activation is not to be expected. Furthermore, due to the biphasic nature of the increase in some factors, such as ANF and BNP, the timing of sampling is critical: later sampling (third day or later) is probably preferable to sampling on admission.²¹ Of the factors measured to date, only BNP⁶⁴ and NT-ANP⁶⁵ have the predictive accuracy required (with a sensitivity of over 80%) for identifying an echocardiographic ejection fraction of less than 40%. Unfortunately, the normal range for these peptides varies considerably between laboratories and caution should be exercised in using published data for local clinical use. The reproducibility of echocardiographic ejection fraction is also questionable.⁶⁶

Table 1 outlines the studies exploring the ability of neuroendocrine measurements to

Table 2 Predictive value of clinical and neuroendocrine indices after myocardial infarction

Study	Variable	Deaths/total < cut off 100% - (%) = PVNT	Deaths/total > cut off with (PVPT)	Sensitivity	Specificity
Svanegaard 1992 ⁵⁷	ANF	3/22 (14%)	16/33 (48%)	84%	53%
	Killip class	4/24 (17%)	15/31 (48%)	70%	56%
Omland 1993 ⁶⁰	ANF	2/73 (3%)	15/72 (21%)	88%	55%
Omland 1993 ⁶¹	NT-ANF	2/56 (4%)	13/83 (16%)	87%	44%
Omland 1995 ⁵⁸	Heart failure	10/103 (10%)	20/42 (48%)	67%	81%
	ANF	4/73 (6%)	27/72 (36%)	87%	61%
	Endothelin	8/73 (8%)	24/72 (33%)	79%	58%
	LVEF	2/43 (5%)	13/42 (31%)	87%	53%
Rouleau 1994 ⁶²	Renin	56/421 (10%)	113 (27%)	35%	81%
	Aldosterone	40/333 (12%)	46/201 (20%)	53%	65%
	Noradrenaline	59/414 (14%)	27/120 (20%)	31%	79%
	Adrenaline	76/492 (15%)	10/42 (24%)	12%	93%
	Dopamine	33/406 (15%)	26/128 (20%)	30%	77%
	ANP	16/203 (8%)	70/331 (21%)	81%	42%
	ADH	54/388 (14%)	32/146 (22%)	37%	75%

PVNT, predictive value of a negative test; PVPT, predictive value of a positive test; ANF, atrial natriuretic factor; NT, N-terminal; LVEF, left ventricular ejection fraction; ADH, antidiuretic hormone.

predict prognosis. Table 2 shows the sensitivity, specificity, and predictive value for mortality based on neuroendocrine variables.

Plasma concentrations of ANF—and possibly endothelin—above the median identify half of the population that has a one-year mortality rate of < 5%, even if the ejection fraction is low.⁶² Thus simple measurement of a neuroendocrine variable could identify a large part of the population which was at low risk and did not need further investigation. On the other hand, the mortality of patients with ANF above the median is probably about 20% at one year. This would appear to be a population at sufficiently high risk to warrant aggressive management.

Currently only NT-ANF has been suggested to carry prognostic information over and above ventricular ejection fraction. However, it is possible that some neuroendocrine variables may be simpler and less expensive to measure than ejection fraction, in which case the onus would be on the latter to prove predictive superiority.

Another possibility is that a large proportion of patients with ventricular dysfunction are at low risk of events. Can neuroendocrine measurements supplement the information contained in the ejection fraction? Data from the SAVE study would suggest so.⁶² Of 534 patients with an ejection fraction of < 40%, only 86 (16%) died during follow up. Thirty eight per cent of this population had a plasma ANF in the normal range. Cardiovascular mortality in these patients was only 4% at one year compared to 12% in those with raised ANF ($P < 0.005$).

Conclusion

Studying and understanding neuroendocrine activation after myocardial infarction and in heart failure is likely to lead to greater insights into the pathophysiology of disease and hopefully to the development of better treatment. Neuroendocrine activation also has a potentially important role in diagnosis, monitoring treatment, and evaluating prognosis in patients with ventricular dysfunction and heart failure. However, much more clinical data are required before measurement of neuroendocrine variables can be recommended in clinical practice. Measurement of NT-ANF can be performed on routine blood specimens,⁶⁷ unlike most other neuroendocrine variables, and hence is more likely to be useful in clinical practice. As many doctors would consider that all patients with major ventricular dysfunction or heart failure should have an echocardiogram to define the nature of the cardiac damage anyway, neuroendocrine markers should be scrutinised for their ability to rule out ventricular dysfunction rather than to detect it.

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