Cardiology Lab Essentials
Chapter 3

NATRIURETIC PEPTIDES AND HEART FAILURE

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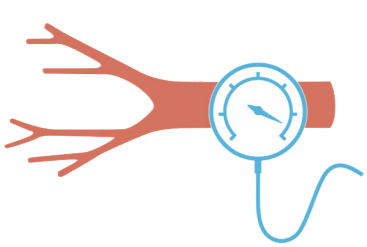
LEARNING HOW HEART FAILURE DEVELOPS

In heart failure, the heart is not able to adequately supply the peripheral tissue with enough oxygenated blood volume.
This may result from

- Impaired cardiac output
- Inability to adequately meet high oxygen demand in the periphery.

These issues can arise from a variety of heart conditions, or from systemic issues.

The two main causes of heart failure



Arterial hypertension

Coronary artery disease

Cardiac output

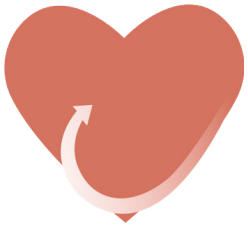
Cardiac output is defined as the amount of blood that the heart pumps in one minute.

Four factors affecting cardiac output

Contractility

Heart rate

Preload



Afterload

Development of heart failure

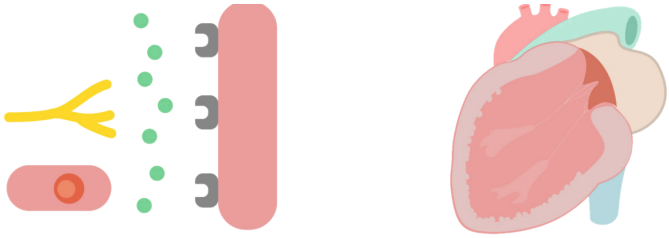
Any disorder that causes long-term impairment to one of these four factors is a potential cause of heart failure.

If the heart has a hard time keeping up with the body's oxygen demands, it tries to cope by using several compensatory mechanisms. In the beginning, these work out fine. However, long-term, these mechanisms start a vicious circle leading to more and more damage.

Compensatory mechanisms

We can generally see two types of compensatory changes

- Neurohumoral changes
- Structural changes



Neurohumoral changes

When the cardiac output is low, blood pressure drops. The activation of several systems aims at increasing blood pressure again.

S**ympathetic nervous system** leads to increased contractility, an increased heart rate as well as vasoconstriction, which increases the afterload.

R**enin-angiotensin-aldosterone system (RAAS)** leads to vasoconstriction as well as sodium and water retention, resulting in increases in both the preload and afterload.

The release of **antidiuretic hormone (ADH)** induces water retention. This leads to an increase in preload and afterload.

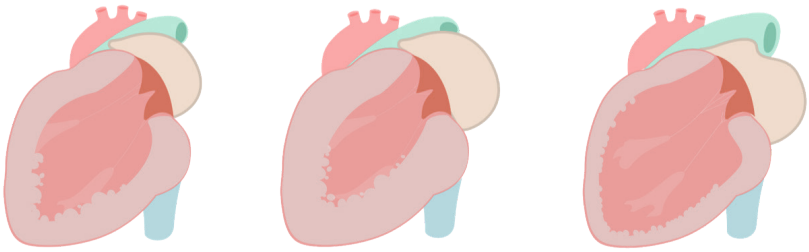
Release of the hormone **endothelin** leads to vasoconstriction, resulting in increased afterload.

To keep the entire system in balance, **natriuretic peptides** are released from atrial and ventricular myocytes. These hormones oppose the renin-angiotensin-aldosterone system by promoting sodium and water excretion and vasodilation. Thus, natriuretic peptides aim to decrease the preload and afterload.

Structural changes

The persistent hemodynamic overload induces adaptations on the molecular and cellular level with altered gene expression and protein synthesis, myocyte hypertrophy, loss of myocytes, fibroblast proliferation, and fibrosis.

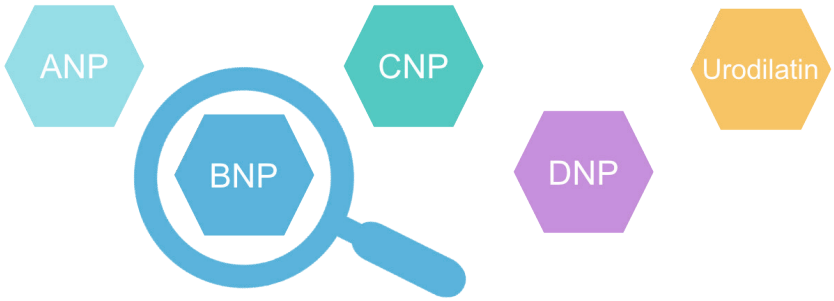
These adaptations lead to structural changes such as hypertrophy or dilation of the myocardium, which in turn impair the cardiac function and support heart failure progression.



Normal Hypertrophy Dilation

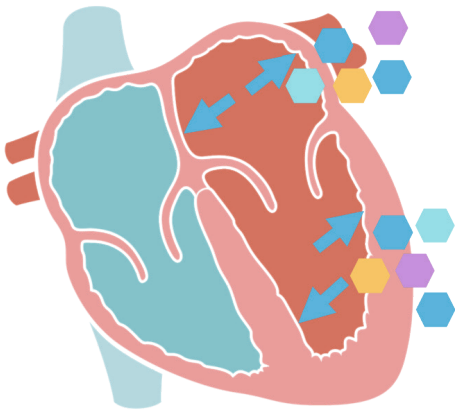
GETTING TO KNOW NATRIURETIC PEPTIDES

There are many members of the natriuretic peptide family.
B-type natriuretic peptide (BNP) is the only natriuretic peptide used in cardiology diagnostics to date.

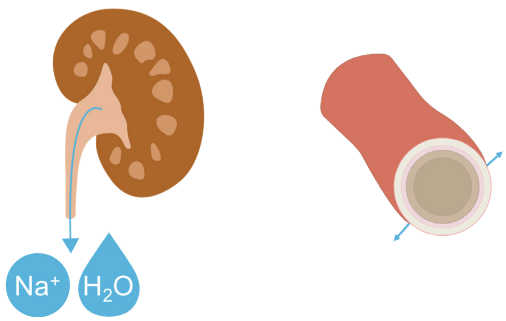


Functions of natriuretic peptides

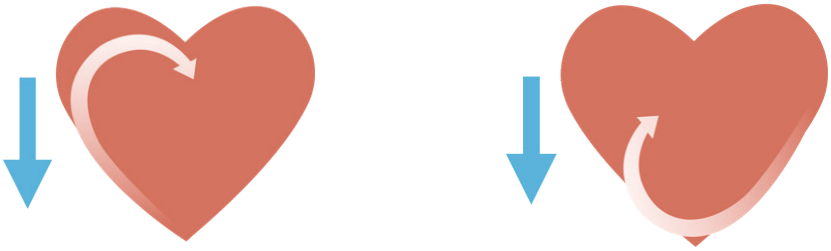
Natriuretic peptide,s like atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), are released in response to increased wall stress in the heart chambers, induced by an increase in circulating blood volume.



They cause sodium and water excretion in the urine, while also inducing vasodilation and therefore, a decrease in vascular resistance.



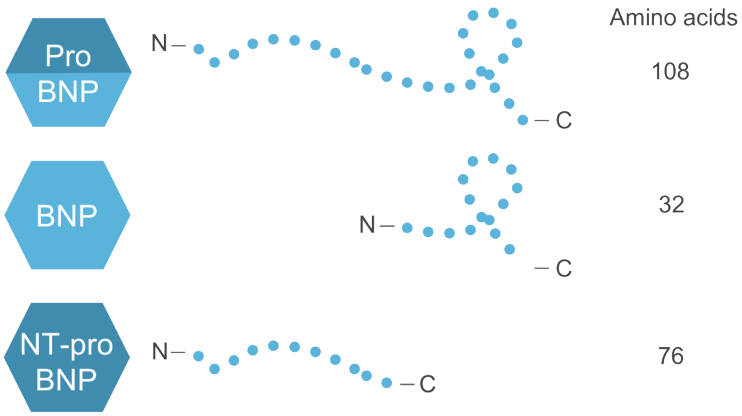
Both actions focus on helping the heart maintain the cardiac output by decreasing the preload and afterload.



Natriuretic peptides have also been shown to offer direct protective effects to the heart by reducing hypertrophy, inhibiting the loss of myocytes, reducing fibrosis, and modulating the immune system.

BNP fragments

A precursor peptide called proBNP is produced in the cell. Upon cellular release proBNP is cleaved into the shorter bioactive BNP and the longer N-terminal fragment of proBNP, which is not biologically active. All of these fragments circulate in the blood.



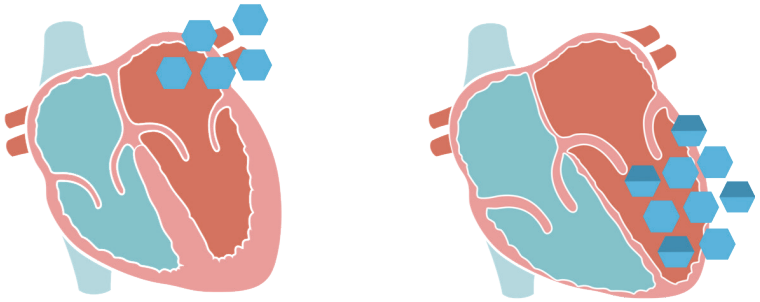
There are commercially available immunoassays for measuring either NT-proBNP or BNP. Both are widely used.

Natriuretic peptides in congestive heart disease

Patients with congestive heart disease present with congestion, sodium retention, and edema despite elevated BNP levels, which should actually counteract these symptoms. Thus, the BNP system must be impaired in congestive heart disease.

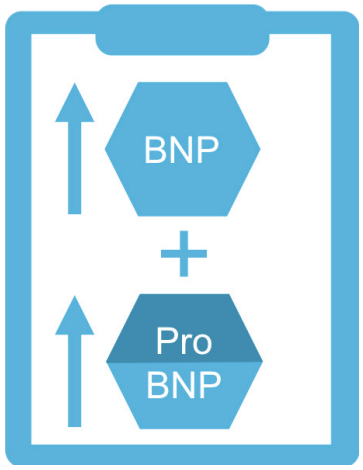
There are two observations that may explain this endocrine paradox.

In healthy individuals, BNP is mainly produced in the atria, whereas in ventricular disease, BNP is mainly produced in the ventricle. It has also been shown that the BNP released from the ventricle of diseased hearts is insufficiently processed, meaning that, in addition to producing more active BNP, patients with heart failure also produce more of the inactive precursor proBNP than healthy patients.



Healthy Diseased

At the same time, we know that the antibodies used in BNP assays bind not only to BNP, but also to the inactive precursor proBNP. Therefore, the levels of BNP reported on our lab reports actually reflect the combined levels of proBNP and BNP. Since we know that proBNP release is increased in heart failure patients, it is likely that, when testing for BNP, the increased levels we see on a lab report actually reflect an increase in the production of this inactive precursor, and not just an increase in production of the bioactive BNP itself.



This would explain why patients with heart failure are unable to induce sufficient natriuresis in order to overcome their volume overload.

Taken together, heart failure can actually be characterized by a dysfunctional natriuretic peptide system.

DIAGNOSING HEART FAILURE WITH NATRIURETIC PEPTIDES

The main indication for natriuretic peptide testing is establishing the presence of acute or chronic heart failure.

Major guidelines agree that natriuretic peptides play an important role in the prevention, diagnosis, and prognosis of heart failure.

Prevention

The role of natriuretic peptides in detecting incident heart failure is still being evaluated. The first large-scale trials showed that natriuretic peptide testing in asymptomatic patients with cardiovascular risk factors, like hypertension and diabetes, predicted the future development of heart failure.

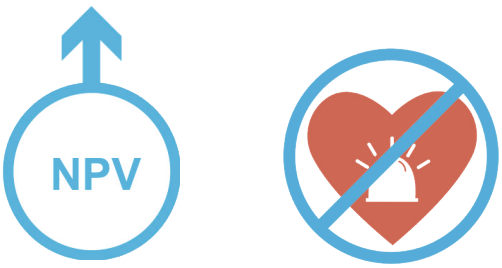
Diagnosis

The strongest mainstay of natriuretic peptide testing is the diagnosis of heart failure.

Diagnosing acute heart failure

Patients with acute symptoms of heart failure most often present in the emergency department with dyspnea. However, dyspnea can have many causes. So, it is not always clear whether the patient is suffering from acute heart failure or another condition. Natriuretic peptide testing plays an important part in the work-up of these patients.

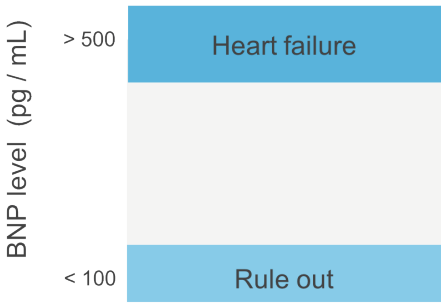
Natriuretic peptide tests are known for their high negative predictive value. Thus, natriuretic peptide testing is useful to rule out the diagnosis of heart failure. However, the positive predictive value is modest, so is not so good at ruling in heart failure. Consequently, positive results should be seen as an add-on supporting other positive diagnostic tests and signs.



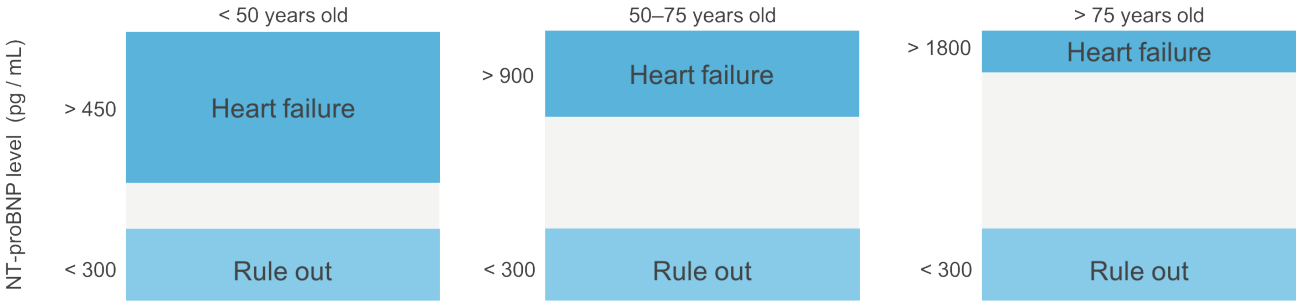
The best situation to test for natriuretic peptides is in dyspnea patients in whom the clinician is ambivalent. If heart failure is very likely or very unlikely, natriuretic peptide measurement shows no substantial additional benefit.

Cutoffs

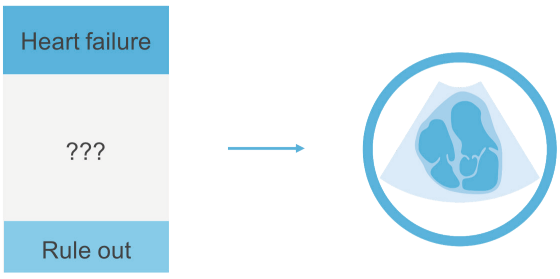
When measuring BNP, values below 100 pg / mL can rule out heart failure as the cause of dyspnea. Values above 500 pg / mL indicate existing heart failure.



When measuring NT-proBNP, values below 300 pg / mL rule out heart failure as the cause of dyspnea. There are age-related cutoffs for NT-proBNP that suggest heart failure.



When the patient's results are between these cutoff levels, no decision can be made based on natriuretic peptides. In these cases, we have to rely on other tools, such as echocardiography, in order to make the diagnosis of heart failure.

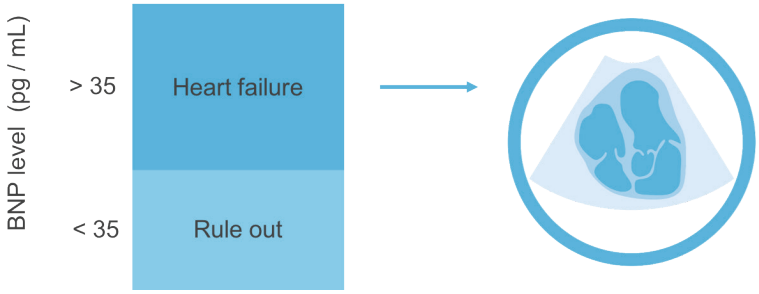


Diagnosing chronic heart failure

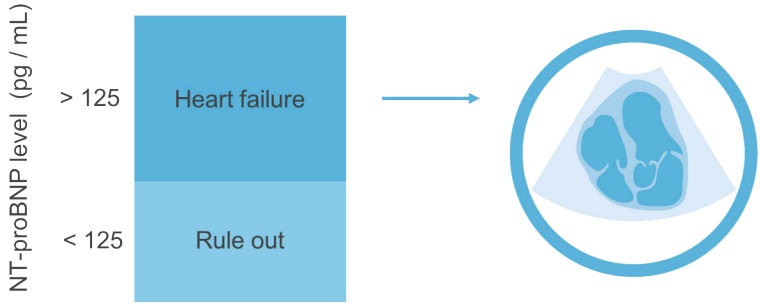
Patients with chronic heart failure mainly present in an outpatient clinic or other primary care facilities.

Natriuretic peptide testing should be performed in patients with a high pre-test probability of having heart failure, based on their physical exam, medical history or conspicuous ECG findings.

Cutoffs
When measuring BNP, values below 35 pg / mL can rule out heart failure while values above 35 pg / mL require initiation of echocardiography to confirm the diagnosis of heart failure.



When measuring NT-proBNP, values below 125 pg / mL rule out heart failure as the cause of dyspnea. Similar to BNP, values above 125 pg / mL require additional echocardiographic evidence in order to diagnose heart failure.

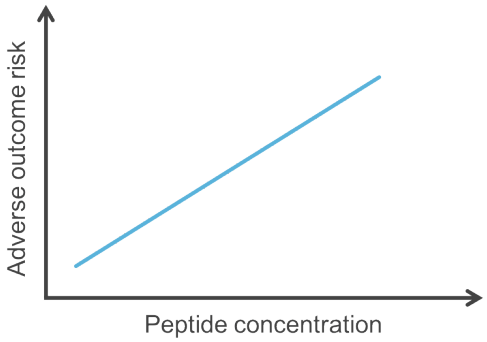


These rules apply for heart failure with reduced as well as with preserved ventricular function.

The European Society of Cardiology goes so far as to recommend that further imaging studies are not necessary in non-acute patients with natriuretic peptide levels below the cutoff as these levels, alone, rule out heart failure very well. (**Reference: *Ponikowski et al., 2016***)

Prognosis

Several studies have shown that the higher the natriuretic peptide concentration, the greater the risk for adverse outcome and mortality.



Other reasons for elevated natriuretic peptide levels

In addition to heart failure, other processes that stress the heart can also lead to elevated natriuretic peptide levels.

These include

- Coronary heart disease
- Valvular heart disease
- Pericarditis
- Pulmonary hypertension
- Renal failure
- Sepsis

INTERPRETING LABS AFTER NEPRILYSIN INHIBITOR TREATMENT

There have been two distinct approaches to support the natriuretic peptide system pharmacologically in heart failure treatment.

The first approach was to supplement BNP with a synthetically produced BNP compound called nesiritide. Intravenous administration of nesiritide induces diuresis, natriuresis, and vasodilation, similar to endogenous BNP.

The second approach aims at increasing BNP by inhibiting BNP breakdown. For this purpose, a new class of drugs has been established that inhibit the neprilysin, the enzyme responsible for BNP metabolism. Neprilysin inhibitors have been successfully combined with angiotensin receptor blockers to form a class of drugs, which is abbreviated ARNI.

ARNIs have been shown to be superior to angiotensin converting enzyme (ACE) inhibitors or monotherapy with angiotensin receptor blockers in chronic heart failure patients with reduced ventricular function. Therefore, ARNIs are the recommended drug therapy of choice in these patients. A history of angioedema is an important contraindication for the use of ARNIs.

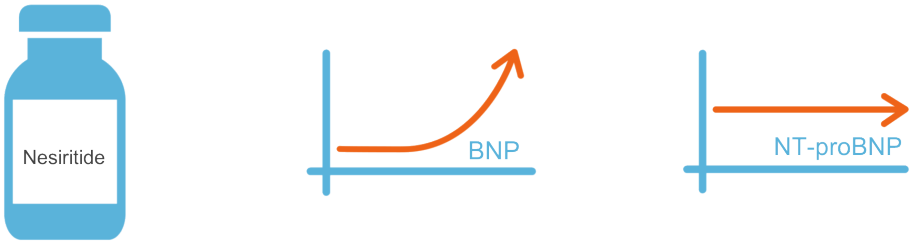
Alterations in natriuretic peptide levels

Since these drugs interfere with natriuretic peptides in the body, it is important to understand how they affect lab results from BNP and NT-proBNP testing.

Nesiritide

Administration of the synthetic BNP, nesiritide, leads to an increase in plasma BNP, which can be detected in the lab. Obviously, this elevation is artificial and does not reflect actual heart damage.

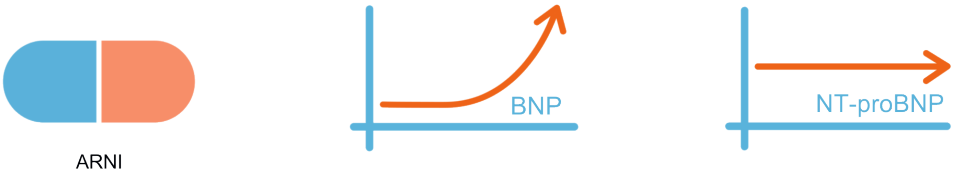
NT-proBNP levels on the other hand are not affected, since nesiritide does not contain NT-pro BNP.



ARNI

Since ARNIs inhibit the degradation of BNP, endogenous BNP is elevated in patients taking these drugs. Again, this elevation does not reflect heart muscle damage.

Neprilysin does not degrade NT-proBNP, so ARNI treatment does not affect NT-proBNP levels in the blood. This means that increased NT-proBNP levels in patients on ARNIs do indicate heart muscle damage.



Experts still advise that BNP measurements can be used to diagnose heart failure in patients on ARNIs. Drug-induced BNP elevations are rather modest, so they do not compromise the ability to rule out heart failure or significantly impact the ability to rule in heart failure in most patients.

The use of BNP for therapy guidance is not yet fully evaluated in patients taking these medications. However, experts advise to wait one month after starting ARNIs, to allow BNP levels to reach a new steady state, and then repeat BNP testing to establish a new baseline value for further monitoring.

NT-proBNP is a good lab marker to diagnose heart failure as well as to monitor heart failure patients. The concept, *the lower the NT-proBNP test results the better* is applicable for all patients, whether on ARNIs or not.

AVOIDING PITFALLS

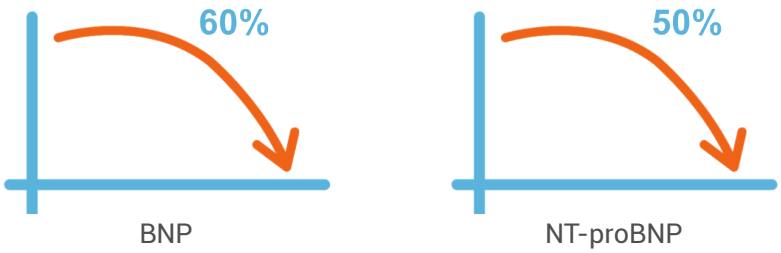
Four factors can influence natriuretic peptide test results

- Intra-individual biological variability
- In vitro stability
- Influencing factors
- Renal failure

Intra-individual biological variability

Both BNP and NT-proBNP show a high level of variability. This means that, physiologically, serial values obtained from the same patient can vary substantially.

From one week to another, only a decline of more than 60% in BNP and a decline of more than 50% in NT-proBNP, is considered clinically significant.



Thus, only marked changes are relevant for clinical outcome and frequent blood sampling is not necessary.

In vitro stability

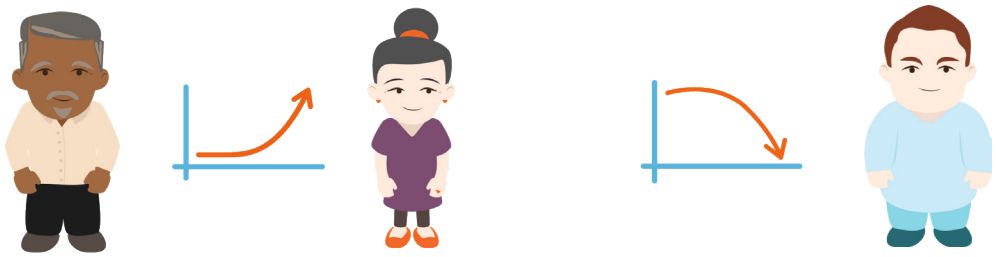
BNP and NT-proBNP differ in their in vitro stability.

NT-proBNP is stable in centrifuged plasma for two days or longer at room temperature. On the other hand, BNP starts to degrade after only about four hours at room temperature. Planning a time-optimal process of transport and analysis in the lab can be crucial in natriuretic peptide testing.

Influencing factors

Natriuretic peptide levels are naturally higher in older people as well as in women compared to men. Thus, age- and gender-related reference values should be used, if provided by the manufacturer.

Interestingly, natriuretic peptide levels are generally lower in obese individuals.



Renal failure

Natriuretic peptide levels rise with an increase in the severity of kidney disease. These elevations predominantly result from actual cardiac pathologies such as cardiovascular disease. Consequently, natriuretic peptides are still useful biomarkers for the diagnosis of heart failure in chronic kidney disease. However, higher cutoff levels should be applied in patients with chronic kidney disease than in patients with normal renal function.

The European Society of Cardiology recommends the following cutoffs to rule out heart failure in patients with a glomerular filtration rate (GFR) < 60 mL / min / 1.73m^2 and BNP: 200–225 ng / L and NT-proBNP: 1200 ng / L
(Reference: *Thygesen et al., 2012*)

READING LIST

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