Neurohormonal response in heart failure and effects of beta-blockers on blood-pressure, heart rate variability and NT-proBNP plasma levels in a patient with newly diagnosed heart failure

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Abstract

Understanding the mechanisms of neurohormonal response and pathophysiologic changes in heart failure is important. All three of these mechanisms (hemodynamic, inflammatory and remodeling) are complex and dependent on one another. In the short term, they will offer support (by favourising a normal cardiac output and a normal blood pressure), that will have the potential to become maladaptive in the long term, leading to edema, pulmonary congestion, the decrease of the cardiac output and myocardial necrosis.Classically used as antihypertensives, beta-blockers can in selected cases promote a minor increase in the blood-pressure, through means of improving heart failure. Furthermore they can induce a significant increase in heart rate variability. Both these processes may occur due to an increased sympathetic outflow from the central nervous system, caused as a „defense" mechanism for the administration of beta-blockers. It is therefore important to study whether beta-blockers exert such a dual action on cardiac autonomic nervous control.

Keywords: heart failure, beta-blockers, heart rate variability

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Case report – Effects of beta-blockers on blood-pressure, heart rate variability and NT-proBNP plasma levels in a patient with newly diagnosed heart failure

A 53-year-old man presented to the hospital with two months of history of dyspnea. His symptoms began gradually, with a prodromal history of headache. His dyspnea had worsened and activities of any kind exacerbated his symptoms, but not lying down. He admitted to chronic alcoholism. His blood pressure was varying at the low end of normal and he presented minor heart rate variability, with overt tachycardia.

He had no allergies to his knowledge and was not taking any drugs. He had no significant past medical history. No family history of cardiomyopathy was reported.

A chest X-ray was performed, which showed a large cardiac shadow. The cardiac ultrasound showed no

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pericardial effusion, but revealed a globally dilated and hypokinetic left ventricle.

A diagnosis of dilated cardiomyopathy secondary to alcoholism with a severe systolic dysfunction (LVEF = 16%) was made on the basis of the medical history. He was started on diuretics (furosemide and spironolactone), ramipril and bisoprolol.

We searched for changes in blood-pressure, heart rate variability and NT-proBNP plasma levels in response to the administration of beta-blockers in a treatment-naïve patient.

Blood-pressure. Before the patient developed dilated cardiomyopathy, he took measures of his blood pressure using an electronic tensiometer, once a week, for at least half a year. After he was admitted to the cardiology ward and began the treatment with beta-blockers (bisoprolol), the blood-pressure measurement was done by medical qualified personnel.

Heart-rate variability was assessed by 24h Holter ECG monitoring.

Analysis of the NT-proBNP plasma levels. After admission to the hospital, several NT-proBNP tests were performed both at baseline and after the start of therapy.

While the blood pressure varied between 100/70 mmHg and 115/80 mmHg before the patient started the beta-blockade treatment, the values showed a slight increase after the treatment was administered, between 120/80 mmHg and 145/105 mmHg.

Furthermore, beta-blockers induced a significant increase in heart rate variability, as assessed by Holter ECG monitoring. The average 24h high frequency power increased by 62% after bisoprolol. Mean heart rate was 58 bpm.

NT-proBNP plasma levels decreased due to the beta-blockade treatment. At the admission to the hospital, the patient had the NT-proBNP plasma levels of >5000 pg/mL, and 2 weeks after initiation of beta-blockers they dropped to ˜ 600 pg/mL.

To sum up, the case study led to three major conclusions regarding the beta-blockade treatment in heart failure: 1) beta-blockers promoted a minor increase in the blood-pressure in a patient not suffering from hypertension; 2) beta-blockers induced a significant increase in heart rate variability; and 3) beta-blockers decreased the initially high NT-proBNP plasma levels.

Discussion

Heart failure leads to the activation of three major compensatory mechanisms, with the purpose to maintain the cardiovascular homeostasis. Although, initially, they have a compensatory role, they quickly turn into vicious circles, which aggravate the cardiac dysfunction.

These three mechanisms are: the hemodynamic mechanism, the inflammatory mechanism and the remodeling mechanism.

The hemodynamic mechanism

It consists of the activation of the sympathetic nervous system and renin-angiotensin system (RAS). They are both responsible for maintaining cardiac output through: increased retention of salt and water, increased contractility and peripheral arterial vasoconstriction.

The activation of the sympathetic nervous system:

The excitatory reflexes have recently been proved to play a role in the excessive activation of the sympathetic nervous system, although it used to be thought that this occurs because of the lack of inhibitory input from arterial or cardiopulmonary baroreceptor reflexes. The main excitatory inputs to sympathetic outflow are discharges from nonbaroreflex peripheral chemoreceptors and muscle metaboreceptors. Therefore, as far as the patients with heart failure are concerned, inhibitory input from baroreceptors decresease and excitatory input increases. The overall result is a higher sympathetic activity.

As a result of the increase in the sympathetic nerve traffic, there is an increase in circulating levels of noradrenalin. In patients with advanced heart failure, the circulating levels of noradrenalin at rest are two-three times bigger than the circulating levels of noradrenalin at rest in patients who do not suffer from heart failure. Indeed, plasma levels of noradrenalin predict mortality in patients with heart failure.

Normally, the source of adrenaline of the healthy heart is the arterial blood. However, in patients with mild heart failure, the noradrenalin in the coronary sinus was proved to be in higher concentration than in the arterial blood, which indicates increased adrenergic stimulation of the heart.

However, as the patients develop advanced heart failure, the myocardial concentration of noradrenalin decreases. This depletion is caused by something that is called the „exhaustion" phenomenon, resulting from prolonged adrenergic activation of the cardiac adrenergic nerves in heart failure. The decreased activity of the myocardial tyrosine hydroxylase (enzyme with a role in the synthesis of noradrenalin) may also play a part.

The depletion of myocardial concentration of noradrenalin is accompanied with a decrease in the number of beta1-adrenergic receptors, a phenomenon which is called „down-regulation". The process can be countered through administration of beta-blockers, which will lead to the restoration of the density of the receptors and the contractile response to the catecholamines.

This phenomenon is most likely mediated by the increase of the circulating levels of noradrenalin near the receptors. Additionally, an increase in the expression of the beta-adrenergic receptor kinase 1 (β-ARK1) can be observed. β-ARK1 phosphorylates the intracytoplasmatic loop of the receptor, increasing its affinity to beta-arrestin. The binding of beta-arrestin leads to the internalization of the receptor. Although, initially, this internalization is a first step in the recycling of the beta-receptors, followed by their reactivation, at some point, the balance will tend to incline towards the traffic of the receptors to the lysosomes, with the purpose of their degradation (as it happens in heart failure).

So, at first, the activation of the sympathetic nervous system will lead to increased contractility, increased relaxation and increased heart rate, all leading to a normal cardiac output.

In the long term, due to these changes, the myocardial necessary of oxygen will be increased, without a proper uptake to counter the necessary. This will lead to the intensification of ischemia, with the apparition of necrosis. Ventricular tachycardia or sudden death can also appear.

The activation of the sympathetic nervous system will also affect the renal and vascular function. In the kidneys, it induces arterial and venous vasoconstriction, with the activation of the renin-angiotensin system, leading to an increase in salt and water retention. In the peripheral vessels, it induces vasoconstriction and vascular hypertrophy.

The activation of the renin-angiotensin system:

In heart failure, the components of the renin-angiotensin system will activate later than those of the sympathetic nervous system.

Increased renin release from the juxtaglomerular apparatus is stimulated by renal hypoperfusion in the afferent arteriole, renal beta-receptors and decreased filtered sodium reaching the macula densa. The renin cleaves the circulating angiotensinogen, synthesized in the liver, forming the angiontensin I (a decapeptide). Angiotensin I is transformed in angiotensin II (an octapeptide), on one hand, by the angiotensin-converting enzyme (ACE) synthesized in lungs and other tissues, and on the other hand by enzymes like kallikrein, trypsin and cathepsin G. This might explain why, in some cases, the ACE inhibitors administered in patients with heart failure are not efficient.

Angiotensin II exerts its biological effects by binding to two types of receptors: angiotensin type 1 (AT1) and angiotensin type 2 (AT2). The AT1 receptor is more abundant in the vessels, while the AT2 receptor is more abundant in the myocardium. While the activation of the AT1 receptor leads to vasoconstriction, stimulation of the bulbar vasomotor center, an increase in the secretion of catecholamines, cell growth and aldosterone secretion, the activation of the AT2 receptor leads to vasodilatation (as a result of an increase in the NO synthesis), inhibition of the cell growth, natriuresis and bradykinin release.

Aldosterone represents another key element of the renin-angiotensin system. It leads to retention of salt and water, and also augments the effects of the angiotensin II, mediated by the AT1 receptors, leading to an increase in vascular inflammation, oxidative stress, endothelial dysfunction and myocytes apoptosis. These all will lead to a worsening of the heart failure, by an increased afterload.

The plasma kallikrein-kinin system plays an important part in vasodilatation. It consists in a number of proteases (kallikrein), that convert the kinin in kininogen. The kallikrein transforms the kininogen synthesized in the liver into bradykinin, a potent vasodilator, leading to accumulation of fluid in the interstitium.

Angiotensin-converting enzyme (ACE), the same that metabolizes angiotensin I in angiotensin II, also metabolizes bradykinin into inactive peptides, reducing the vasodilatation.

The inflammatory mechanism

It has been recently discovered that proinflammatory cytokines may play an important part into the pathogenesis of the heart failure. For years they have been thought to be produced only by the immune system, but now it is recognized that they are also produced locally within the myocardium, in response to cardiac injury. Although, at first, they play a part defending the organism against microbes and foreign bodies, in time they lead to maladaptive changes. Tumor necrosis factor and IL-6 (both proinflammatory cytokines) are increased in patients with heart failure and correlate with adverse patient outcomes. They lead to alterations in the biology of the myocyte, such as myocyte hypertrophy, negative inotropic effects, increased oxidative stress and, in the end, necrosis and apoptosis. They also stimulate the conversion of fibroblasts to myofibroblasts and the upregulation of AT1 receptors on fibroblasts.

The remodeling mechanism

A number of studies have suggested that failing cardiac myocytes undergo important changes that lead to a progressive loss of contractile function. These changes are represented by a decreased α-MHC gene expression with a concomitant increase in β-MHC expression, alterations in cytoskeletal proteins, desensitization of β-adrenergic signaling and loss of myofilaments.

In response to the hemodynamic overload, the heart will answer in two different ways. In pressure overload hypertrophy, the systolic wall stress will increase, leading to an addition of the sarcomeres in parallel. This pattern of remodeling is referred to as concentric hypertrophy. In contrast, in volume overload hypertrophy, the diastolic wall stress will increase, leading to an addition of the sarcomeres in series. This pattern of remodeling is reffered to as eccentric hypertrophy.

Myocyte hypertrophy also leads to changes in the biologic phenotype of the myocyte, due to the reactivation of genes normally not expressed postnatally. This fetal gene program is also accompanied by a decrease in the expression of a number of genes that are normally expressed in the adult heart. There are several stimuli for this genetic reprogramming of the myocyte, including mechanical stretch strain of the myocyte, noradrenalin, angiotensin II and inflammatory cytokines.

Initially, the myocyte hypertrophy is characterized by an increase in the number of myofibrils and mitochondria. At this stage, although the myocytes are bigger than usual, they are still well-organized. This explains why, at first, the myocyte hypertrophy works as an adaptive change and maintains a normal cardiac output. In the later stages, though, the cardiomyocytes will lose their contractile elements and will show obvious disruptions in cellular organization, leading to necrosis and apoptosis.

Conclusions

Understanding the mechanisms of neurohormonal response and pathophysiologic changes in heart failure is important. All three of these mechanisms (hemodynamic, inflammatory and remodeling) are complex and dependent on one another. In the short term, they will offer support (by favourising a normal cardiac output and a normal blood pressure), support that will have the potential to become maladaptive in the long term, leading to edema, pulmonary congestion, the decrease of the cardiac output and myocardial necrosis.

However, these mechanisms are just the tip of the iceberg. Many more are to be discovered and maybe even reconsidered in the field of heart failure and administration of beta-blockers.

Classically used as antihypertensives, there are some rare cases in which they promote a minor increase in the blood-pressure, through means of improving heart failure. Furthermore they can induce a significant increase in heart rate variability. Both these processes may occur due to an increased sympathetic outflow from the central nervous system, caused as a „defense" mechanism for the administration of beta-blockers. It is therefore important to study whether beta-blockers exert such a dual action on cardiac autonomic nervous control.

Conflict of interests

There are no conflicts of interests.

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