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REVIEW FOR EXPERTS
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Human tissue kallikrein and kinins in systolic heart failure: an overview

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Introduction

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the pumping capacity of the heart. A variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin-aldosterone system (RAAS) and the cytokine system, all of which have been extensively studied[1]. However, there is little information on the participation of the kallikrein-kinin system (KKS), in HF.

Kallikreins (EC 3.4.21.8) are key—enzymes in the KKS, constituting a subgroup of the serine protease family known to have several physiological functions[2]. The kallikreins are found in glandular cells, neutrophils and biological fluids and can be divided into two main groups: plasma (EC 3.4.21.3 4) and tissue (EC 3.4.21.35) kallikreins[3]. The KLK1 gene, located on chromosome 19q13.4, expresses human tissue kallikrein (hK1)[4], the principal known biochemical function of which is releasing the vasoactive and spasmogenic decapeptide kallidin (Lys-bradykinin) (Lys-BK) from the plasma protein low-molecular-weigh kininogen[5]. The KLK1 gene expression is highest in the pancreas, kidney and salivary glands, but also in prostate, breast, testis, uterus, heart and central nervous system[4]. Renal kallikrein is believed to release kinins in the distal nephron[6]. Accumulative evidence suggests that renal KKS may play a role in the regulation of renal function and in certain diseases such as hypertension[7]. The role of KKS in HF is not clear yet.

Kinins and heart failure

Kinins (BK and Lys-BK) are active peptides released as a result of the enzymatic activity of kallikreins on kininogens[3]. Kinins have cardio-protective effects, such as vasodilatation, hypotension, release of endothelial relaxation factors - nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF), natriuresis[3,8]. These peptides are rapidly inactivated by the kininases I and II. Kininase II is also known as the angiotensin converting enzyme (ACE). It is believed that some of the deleterious effects of ACE could be due to the inactivation of BK and that, on the other hand, its beneficial actions would derive from the extended availability of those peptides[9]. There is experimental evidence for the increasing of BK in HF.

Cheng et al.[10] determined the level and functional effects of endogenous BK in 8 instrumented conscious dogs, both before and after pacing-induced HF. The authors concluded that, before HF, endogenous BK results in coronary dilation, but has no effect on systemic arterial vasodilatation or cardiac performance. After HF, endogenous BK is significantly increased, and, acting through B_2-receptors produces coronary and arterial vasodilatation, and improves left ventricular (LV) relation and contractile performance. Thus, endogenous BK may play an important role in preserving cardiovascular function in HF. Davie et al.[11] tried to define the role of BK in 12 HF patients who received enalapril and losartan or the inverse. They occluded forearm veins and measured blood flow through pletismography during intra-brachial infusion of BK. The measures were made before and after the intra-brachial infusion of HOE-140. The authors concluded that BK causes intense vasodilatation in HF patients and that this is more intense in those using ACE inhibitors (ACEI), suggesting that the beneficial effects of these drugs might be related to the potentiation of BK effects.

Cugno et al.[12] evaluated the plasma KKS by measuring plasma BK levels in 21 chronic and stable HF patients and 18 healthy controls. They measured BK, plasma renin activity (PRA), atrial natriuretic peptide (ANP) and tumor necrosis factor (TNF). The authors observed that serum levels of TNF, ANP and PRA were significantly higher in HF patients than in controls but there was no statistically significant difference in BK levels.

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Campbell[13] measured kinin peptides (BK and Lys-BK) in individuals with severe HF, who were receiving maximally tolerated doses of ACE inhibitor therapy. In comparison with non-HF individuals having coronary artery disease, HF patients did not show increased levels of BK in arterial blood, and the levels of Lys-BK in their blood were suppressed to a level below detection in the assay. According to the author, the suppression of blood Lys-BK level suggests that the activity of tissue KKS (and possibly plasma KKS) may be suppressed in severe HF. Recently Ryan et al.[14] hypothesized that LV remodeling and matrix loss in volume overload (VO) are mediated by BK and exacerbated by chronic ACE inhibition. Echocardiography, LV collagen content, and isolated cardiomyocytes were studied in rats after VO by aortocaval fistula (ACF) of 12 h, 2 and 5 days, and 4, 8, and 15 weeks. They also studied ACF rats after BK_2 receptor (BK_2R) blockade (2 days) or ACE inhibition (4 weeks). The authors concluded that immediately after ACF induction, eccentric LV remodeling is mediated by interstitial collagen loss without cardiomyocyte elongation. Acute BK_2R blockade prevents eccentric LV remodeling and improves function. Chronic ACE inhibition does not prevent eccentric LV remodeling or improve function, suggesting that ACE inhibitor-mediated increase in LV BK exacerbates matrix loss and explains why ACE inhibition is ineffective in VO.

Tissue kallikrein and heart failure

The role of hK1 in human HF is not clear yet. There are few clinical studies, one published by our group, and some other new experimental studies.

Until 1991 there were little information regarding participation of the renal KKS in HF. Guarda et al.[15] evaluated the KKS through urinary kallikrein measurements in 17 HF patients (11 in New York Heart Association -NYHA- classes II and III, and 6 in class IV), who were compared with 10 normal individuals used as controls. Urinary kallikrein activity was estimated from a 24-hour collected urine sample by its amidolytic activity on the chromogenic tripeptide substrate H-D-Val-Leu-pNitroanilide, S-2266. Urinary kallikrein excretion was significantly lower in patients with HF than in controls, and it decreased progressively according to the severity of HF. These patients were taking furosemide. According to the authors, furosemide is known to stimulate urinary kallikrein excretion. It is possible that urinary kallikrein levels determined in their patients could have been influenced by this drug. However, their patients in functional class IV, who received the largest doses of furosemide, had the lowest urinary kallikrein values. The authors suggest that this intrarrenal hormonal system involved in water and electrolyte excretion and renal blood flow regulation may be part of an abnormal neurohumoral axis in HF.

In another study, Ol'binskaia et al.[16] evaluated the morpho-functional characteristics and the activity of KKS in patients with chronic HF during treatment with captopril. All the subjects were coronary patients with HF stage I-III. For stage HF I, urinary kallikrein excretion was similar to that of normal controls, while in stage II-III patients it fell significantly. Captopril induced a drop in relevant secretion of stage I and a rise for stage II-III subjects.

Godoy et al.[17] studied the neurohormonal activity of ACEI in HF patients. Nine patients with idiopathic dilated cardiomyopathy received enalapril during 8 weeks. Before and after treatment period plasma levels of atrial natriuretic peptide (ANP) and BK and urinary excretion of kallikreins (UK) and prostaglandin E2 were measured. With Enalapril therapy, there was a significant decrease in plasma ANP and UK, which could explain some of the clinical benefits observed with ACEI in patients with HF.

Campbell[13] measured kinin peptides in subjects with severe HF who were receiving maximally tolerated doses of ACEI therapy. In comparison with subjects with coronary artery disease without HF, HF subjects did not show increased levels of BK peptides in arterial blood and blood levels of kallidin peptides were suppressed below the level of detection for their assay. This suppression of blood kallidin peptide levels despite ACEI therapy suggests that the activity of the tissue KKS (and possibly plasma KKS) may be suppressed in severe HF.

Agata et al.[18], in an experimental study, used the somatic gene delivery approach to explore the role of the KKS in cardiac remodeling and apoptosis after myocardial infarction (MI). Rats were subjected to coronary artery ligation to induce MI, and adenovirus carrying the hK1 or control luciferase gene was injected into the tail vein at 1 week after surgery. Cardiac output gradually decreased from 2 to 6 weeks after MI, whereas delivery of the kallikrein gene prevented this decrease. Kallikrein significantly improved cardiac remodeling by decreasing collagen density, cardiomyocyte size and LV internal perimeter and increasing capillary density in the heart at 6 weeks after MI. Kallikrein gene transfer attenuated myocardial apoptosis which was positively correlated with remodeling parameters in the heart at 2 weeks after MI. Endothelial dysfunction, characterized by increased vascular resistance, decreased LV blood flow, and decreased cardiac NO levels, existed in remodeled hearts at 2 weeks after MI, whereas kallikrein gene transfer improved these parameters. This study indicates that the KKS plays an important role in preventing the progression of HF by attenuating cardiac hypertrophy and fibrosis, improving endothelial function and inhibiting myocardial apoptosis.

We studied the tissue (renal) KKS activity by measuring the amidase activity of hK1 in the early-morning midstream urine of 28 systolic HF (SHF) human patients who were not receiving ACEI (due to strong clinical contraindications) and 28 healthy control individuals. All patients (median age 56 years) had chronic SHF, with LV ejection fraction £ 40%, in NYHA's functional classes II-IV. Patients had SHF of any etiology, except for hypertension, since it had been already shown that hK1 activity was reduced in hypertensive patients. Ten were male and 18 female, 20 were whites and 8 were blacks. Control subjects were paired according to gender, age ± 5 years and ethnicity. Patients had serum creatinine £ 1.5 mg/dL. All patients with SHF received maximal medical therapy, according to their functional classes and the treatment guidelines recommendations, with 16 (57.1%) using a beta-blocker, 26 (92.9%) an ARB, 27 (93.4%) furosemide, 18 (64.3%) digoxin, 17 (60.7%) spironolactone, and 7 (25%) needed the use of intravenous dobutamine. hK1 amidase activity was assayed spectrophotometrically with H-D-Val-Leu-Arg-Nan substrate. Crea-

tinine was determined by Jaffé's method. hK1 amidase activity was expressed in $mM.min^{-1}.mg^{-1}$ creatinine to correct for differences in urine flow rate. hK1 amidase activity was significantly lower in the urine of SHF patients. In our study 27 from the total of 28 SHF patients were using furosemide. In all patients, urinary hK1 amidase activity was reduced[19].

Ohman and Karlberg[20] observed that furosemide increases the urine volume and the excretion of tissue kallikrein in normotensive individuals and in patients with primary hypertension. Thus the diminished levels of hK1 amidase activity (instead of their expected increasing) in patients treated with furosemide, in our study, could be explained by their having HF[19]. It has been suggested that mineralocorticoid administration increases urinary kallikrein (renal tissue kallikrein) excretion whereas spironolactone decreases it[6]. In our study, 17 of the 28 SHF patients were using spironolactone. It could be supposed that the diminished urinary hK1 amidase activity observed in these patients could be due to the effect of spironolactone. However, comparing patients using and not using the drug, we found no statistically significant difference between hK1 amidase activities in the two groups. There was no statistically significant difference between NYHA's functional classes and hK1 amidase activity. In our study the majority of patients and controls were whites and there was no significant effect of ethnicity on hK1 amidase activity. Our data showed that the KKS, which supposedly protect the cardiovascular system from damages, has its activity diminished in HF, suggesting that the renal KKS is involved in SHF physiopathology[19].

Some experimental studies were published since our publication, regarding ischaemic HF. Spillmann et al.[20] aimed to test the original hypothesis that hK1 gene delivery to the peri-infarct myocardium would prevent post-ischemic HF. They induced MI in anesthetized mice by permanently occluding the left coronary artery. HK1 gene was delivered to the peri-infact (Peri-I) myocardium via an adenoviral vector carrying hK1 cDNA (Ad.hTK). Controls received Ad.null or saline. Capillary and arteriole density were evaluated 14 days post MI in the Peri-I and remote (R) zone. Circulating endothelial progenitor cells (EPCs) in the peripheral blood were determined. Cardiac progenitor cells (CPCs) were identified, 4 and 14 days post MI. Apoptosis of cardiomyocytes from the MI heart was studied *in vivo* and *ex vivo*. Ad.hTK promoted growth of capillaries and arterioles in the Peri-I myocardium, increased the number of EPCs, increased the abundance of CPCs in the Peri-I and suppressed the apoptotic death of Peri-I cardiomyocytes *in vivo* and *ex vivo*. As a consequence of these beneficial effects, Ad.hTK-transduced hearts 5 weeks after MI were protected from post-MI ventricular dilatation and showed better systolic and diastolic functions. This study adds to the knowledge of the protective effects of hK1 gene transfer on ischemic diseases and opens new avenues for the treatment of post-MI cardiac failure.

In another study, Yao et al.[22] investigated the effect of a stable supply of kallikrein and kinin on ventricular remodeling and blood vessel growth in rats after MI. At 1 week after coronary artery ligation, purified tissue kallikrein or kinin was infused through a minipump for 4 weeks. At 5 weeks after MI, kallikrein and kinin infusion significantly improved cardiac contractility and reduced diastolic dysfunction without affecting systolic blood pressure. Kallikrein and kinin infusion significantly increased capillary density in the noninfarcted region. Kallikrein and kinin infusion also reduced heart weight/body weight ratio, cardiomyocyte size and atrial natriuretic peptide and brain natriuretic peptide in the noninfarcted area. Moreover, kallikrein and kinin infusion inhibited interstitial collagen deposition. The effects on cardiac remodeling were associated with increased nitric oxide (NO) levels. These results indicate that a sub-depressor dose of kallikrein or kinin can restore impaired cardiac function in rats with post-MI HF by inhibiting hypertrophy and fibrosis and promoting angiogenesis through increased NO formation.

Recently, Pons et al.[23] aimed to determine whether tissue kallikrein (TK) deficiency in the mouse influences survival and cardiac remodeling after induced MI. They induced MI in 10 week-old male TK-deficient mice and wild-type littermates. Survival was assessed up to 14 months. Cardiac morphological and functional parameters were serially measured by echocardiography. In another experiment, myocardial capillary density and NO content were evaluated at 3 months. Infarct size was similar in both genotypes. MI resulted in severe cardiac dysfunction. Up to 12 months after MI TK-deficient mice displayed an increased mortality rate and aggravation of LV hypertrophy and dilatation by comparison with TK-positive mice. They concluded that TK exerts a protective role in HF in mice, probably related to coronary effects. As partial genetic deficiency in TK activity occurs in humans, TK-deficient subjects may be at increased risk of mortality in HF. The animal models reviewed here make our previously published work[19] even more important, since we showed decreased human tissue (renal) kallikrein activity in human heart failure.

Conclusion

The comprehension of HF physiopathology and, consequently, its treatment objectives have changed over the past three decades. Treatment strategies directed to counter act the deleterious effects of the RAAS have been developed and have changed the mortality rates and quality of life of HF patients. The evidences presented in this paper suggest that the KKS, which antagonizes the RAAS, plays important roles in the physiopathological processes of HF. It seems that the KKS is deficient in this condition and this could be due to genetic abnormalities of hK1 genes, diminished production and release of hK1 or to down-regulation of BK receptors. The disease may be better treated, in the newer future, by the application of tissue kallikrein and/or the use of specific BK-receptor agonists. A new field for the KKS involving angiogenesis-mediated myocardial cells having a stem cell nature is emerging[24]. We think that more clinical studies involving the KKS in cardiovascular diseases, specially HF, should help to develop possible therapeutic options.

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