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PROENKEPHALIN IN HEART FAILURE

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DISCLOSURE STATEMENT

KEYWORDS

Proenkephalin, PENK, Heart failure, Delta opioid receptor, Enkephalin, Renal function

KEY POINTS

- The endogenous opioid system plays an important role in cardioprotection, and is activated in heart failure.
- Proenkephalin is a precursor for endogenous enkephalins which in turn activate delta-opioid receptors in various tissues.
- In the heart, delta-opioid receptor activation results in reduced myocardial contractility, reduced blood pressure and heart rate, but in kidneys increases renal blood flow and urine output.
- Circulating proenkephalin, a surrogate for enkephalin synthesis from proenkephalin, predicts poor outcomes in myocardial infarction and heart failure, and with additional predictive value.
- Adding proenkephalin to a decision making process will help physicians predict risk more accurately, and could improve treatment selection in these patients.

SYNOPSIS

The opioid system is activated in heart failure which may be cardioprotective but may also be counter-regulatory. Recently, systemic proenkephalin activation has been investigated in various conditions predicting mortality and kidney injury. In acute heart failure, proenkephalin independently predicts mortality and heart failure rehospitalisation in addition to traditional risk markers. It also predicts worsening renal function, increasingly recognized as an important risk predictor for poor outcome in heart failure. This review explores the role of enkephalins and delta opioid receptors in the heart, then reviews studies measuring proenkephalin levels in the circulation and their associations with prognosis.

PROENKEPHALIN IN HEART FAILURE

Background

The opioid system has been well studied and characterised in the nervous system, but interest has been mounting on its importance in the cardiovascular system (1). Endogenous opioid peptides which interact with receptors for morphine, subsequently named enkephalins, were first reported by Kosterlitz *et al*. in 1975 (2). Besides Met-and Leu-enkephalin, several other enkephalincontaining peptides have been discovered, all of which have varying degrees of specificity on opioid receptors. Although enkephalins were first characterised in brain and adrenal glands through the use of immunohistochemistry (3), both enkephalins and opioid receptors have since been identified in the central nervous system in the adrenal medulla, dorsal vagus nucleus, nucleus ambiguus, nucleus tractus solitarius, and in the peripheral nervous system in sympathetic and parasympathetic neurones of the heart, spleen, vas deferens, stomach, intestine, lung, pancreas and liver (4, 5).

Opioid peptides arise from pro-opiomelanocortin, prodynorphin and proenkephalin, the precursors for endorphins, dynorphins and enkephalins respectively. These peptides are the endogenous ligands for the three types of opioid receptors, μ-opioid receptors, κ-opioid receptors and δ-opioid receptors respectively (6, 7). These peptides have been found to affect various physiological activities including respiration, sleep, immune function, endocrine function, body temperature, attention, catatonia and drug dependence (8-12).

The opioid system also plays an important role in the cardiovascular system, for which evidence has been accumulating over the past 3 decades. These regulatory roles occur at both the central and peripheral level. Activation of opioid peptide receptors by their respective

endogenous ligands results in different effects on heart rate and blood pressure, depending on the animal species, agonist route, administration and anaesthetic use (13-15). In general, opioid peptide receptor stimulation causes hypotension and bradycardia. However, activation of δ-opioid receptors in the nucleus tractus solitarius or cisterna causes hypertension and tachycardia, whilst activation of the κ-opioid receptors in the same place causes biphasic effects on blood pressure.

In light of recent work on the emerging role of proenkephalin as a marker for prognosis, this review will first focus on the relevance of enkephalins and its precursor proenkephalin in the cardiovascular system, followed by an overview of the emerging evidence for proenkephalin's role in prognosis in heart failure.

Enkephalins in the heart

Although enkephalins are produced and released in the central nervous system and in peripheral neuronal terminals in the heart where they are co-released with catecholamines (4), the majority of enkephalins produced in the heart are from cardiomyocytes (16, 17). Enkephalins are synthesised from preproenkephalin A, which has 267 amino acids (18, 19). Cleavage of the N-terminal signal sequence gives rise to Proenkephalin (243 amino-acids) (20), which subsequently undergoes further post-translational processing to produce 4 Met-enkephalins, 1 Leu-enkephalin, the heptapeptide Met-Enkephalin-Arg-Phe and the octapeptide Met-Enkephalin-Arg-Gly-Lys, as well as other analogues and intermediates (Figure 1). Proenkephalin mRNA has been shown to be higher in heart than brain; however, lower quantities of mature enkephalin peptides can be extracted from the heart (21, 22). Interestingly, most of the enkephalin-containing peptides recovered from rat ventricle are concentrated in larger molecular weight intermediary peptides (23) which could provide a ready source for the myocardium to use to synthesize mature enkephalins in times of need (24). Post-translational

processing of proenkephalin is tissue specific (25) resulting in different intermediates. After synthesis, circulating enkephalins are rapidly degraded by neutral endopeptidases (also known as enkephalinases) (26, 27), giving them a half-life of <15 minutes (28). These membrane-bound endopeptidases are present in cardiomyocytes (29), implying that enkephalins have an autocrine/paracrine effect, being produced and degraded locally as required. However, there are other sites of high enkephalinase activity, such as the kidneys and lungs (30) which could remove circulating enkephalins.

Cardioprotection

Enkephalins have been found to play a role in ischaemic preconditioning. Ischaemic preconditioning describes the protection from ischaemic events following episodes of brief sublethal ischaemia (31), which reduces myocardial infarct size and improves functional recovery. Animal studies with specific opioid peptide receptor antagonism show that ischaemic preconditioning is dependent on δ-opioid receptors but not μ-opioid receptors or κ-opioid receptors (32, 33). Endurance exercise promotes cardiac protection against myocardial ischaemia-reperfusion injury, also through a δ-opioid receptor dependent process, involving down-regulation of δ-opioid receptor and κ-opioid receptor (34). Nevertheless the downstream mechanisms that underpin this cardioprotection are not fully understood, although most evidence implicates cardiac mitochondria (35), where mitochondrial ATP-sensitive potassium channels open to prevent cystosolic calcium overload (36). Activation of δ-opioid receptor and κ-opioid receptor protects cardiomyocytes via mitochondrial potassium-ATP channels (37). Finally, opioid peptide receptor inhibition by naloxone abolishes the cardiac protection offered by ischaemic preconditioning (38, 39). Parallels can be drawn from nature regarding the potential evolutionary benefit for ischaemic preconditioning. Hibernation in cold-weather and ischaemic pre-conditioning share a similar process, both of which can be abolished by δ-opioid

receptor inhibition (40). Further evidence for its relevance is from gene expression profiling of human hibernating myocardium which found increased expression of proenkephalin in these tissues compared to normally-contracting regions (41).

Regulation of cellular life cycle

Enkephalins participate in growth through a different receptor known as the opioid growth factor receptor (OGFr) previously known as the zeta (ζ) opioid receptor. The specific endogenous ligand for this receptor is Met5-Enkephalin, one of 4 Met-enkephalins synthesized from Proenkephalin. These receptors have been shown to be distinct from classical opioid receptors. OGFr activation inhibits normal cell and cancer cell proliferation by inhibiting the G_0/S phases of the cell cycle. The OGFr protein and gene expression has a wide distribution akin to that of enkephalins, of neural and non-neural origin, and has been detected in mouse brain, heart, kidney, liver and muscle (42-44). Much like preproenkephalin, expression levels of the OGFr decline in adult tissues and non-replicative organs (44-46). This OGF-OGFr axis tonically maintains homeostasis of proliferating cells and tissues and requires a change in balance of both components to change cell number. An increase in OGF or OGFr may inhibit cellular proliferation but the converse may be required in cases of wound healing or tissue repair. RNA sequencing of normal human tissues identified that OGFr expression is highest in spleen/lymphoid tissue with average expression in kidney but one of the lowest in heart (47). In addition to suppressing cellular proliferation, proenkephalin facilitates stress-activated apoptosis, a function thought to be due to physical association of endogenous proenkephalin with the transcriptional co-repressor histone deacetylase, following activation of nuclear factor κ-B or p53 pathways (48). Whilst this alludes to the importance that opioids play in cellular proliferation both in physiological and pathophysiological states, with particular importance in

tumorigenesis, whether or not enkephalins significantly regulate cellular proliferation in adult hearts (thought to be post-mitotic) is unclear and warrants further investigation.

Enkephalins in heart failure

The role of the enkephalins in heart failure is not very well characterised and probably complex with activation of the cardiac opioid system in congestive heart failure observed in animals (49). In dogs, increased endogenous opioids during heart failure act on the δ-opioid receptors causing a decrease of myocardial mechanical performance and alter regional blood flow distribution (50). Deranged intracellular calcium signalling and homeostasis have been implicated in heart failure (51, 52). Suppression of the L-type Ca^{2+}-current has been observed in response to enkephalin, resulting in reduced myocardial contractility (53) and δ-opioid receptor activation reduces the responsiveness of myofilaments to Ca^{2+}(54). These opioid receptors are found to co-localize with the L-type Ca^{2+}-channel and the intracellular ryanodine receptor (RyR). Additionally, both proenkephalin and δ-opioid receptor mRNA and their respective proteins were found to be upregulated in the left ventricle in heart failure (55). Heart failure results in systemic sympathetic activation, and there seems to be some dependence of the opioid system on sympathetic activity. In isolated rat hearts, δ-opioid receptor inhibition resulted in increased blood pressure and cardiac contractility, but blockade of adrenergic beta-receptors abolished this effect. This could be due to downstream 'cross-talk' between beta-adrenergic sympathetic signalling and opioid receptor signalling (56). β-endorphin levels are elevated in the ventricles of failing hearts (49), and although the δ-opioid receptor is generally accepted to be principally responsible for regulating the vasopressor/depressor response of opioid peptides in heart failure, the μ-opioid receptor is thought to be responsible for the blunting of baroreceptor sensitivity in heart failure (57).

In humans, β-endorphins have been found to be elevated in congestive heart failure as compared with healthy subjects and these increases were correlated with the patients' New York Heart Association functional cardiac status (control: 14.0 ± 4.4 pg/ml; class II: 17.9 ± 3.6 pg/ml; class III: 28.3 ± 8.8 pg/ml; class IV: 46.7 ± 14.6 pg/ml, mean $\pm$ SD) (58). In addition, in acute heart failure, atrial natriuretic factor (ANF), a neurohormone which causes diuresis, natriuresis and correlates with the severity of heart failure is also positively correlated with circulating opioid peptides (β-endorphin, dynorphin and met-enkephalin). Non-specific opioid receptor inhibition with naloxone significantly increased ANF levels, noradrenaline levels, heart rate and blood pressure in severe heart failure, but in less severe heart failure, naloxone decreased ANF levels, without change to noradrenaline, blood pressure and heart rate (59). The authors hypothesized that this could be due to sympathetic activity dependent upregulation of the opioid system in heart failure, where more severe heart failure results in increased sympathetic activation.

Clinically, morphine is often used for rapid relief of respiratory distress in acute heart failure. Historically this was thought to occur through a reduction in ventricular pre-load, reducing work to the ventricles while other therapies, such as diuretics take effect. Physiological elevations in β-endorphins support this notion, although the survival advantage of lowering systemic blood pressure and heart rate as a result of opioid receptor activation is not immediately clear. Peacock *et al.* performed a retrospective analysis of the Acute Decompensated Heart Failure National Registry (ADHERE) investigating if there was a link between morphine administration in acute heart failure and mortality risk (60). This study found patients receiving morphine had more severe heart failure symptoms with rest dyspnoea, more radiographic evidence of pulmonary congestion and raised troponin. Morphine administration was associated with a higher risk of mechanical ventilation, ICU admissions

and increased mortality. Mortality risk remained even after exclusion of ventilated patients and adjustment with OR of 4.84 (95%CI 4.52-5.18).

Measuring proenkephalin

Ascertaining the activity of the enkephalin system has previously been difficult to perform and interpret, due to the short half-life of active enkephalins and the large number of intermediate peptides, some of which are of large molecular weight and unlikely to be released into the circulation until they have been post-processed into active enkephalins. Human preproenkephalin A comprises 267 amino-acids (AA) and is widely distributed in the nervous system, adrenal medulla, bone derived cells and cells of the immune system. The N-terminal signal peptide is removed by a specific signal peptidase (20), giving rise to a 243AA proenkephalin-A precursor protein (now named Proenkephalin). This precursor can then be targeted by specific membrane-bound carboxypeptidases also known as enkephalin-convertases (61) which cleave the C-terminal basic residues to form mature Met and Leu-enkephalins. Initially identified in adrenal chromaffin cells, they have also been measured in brain, with co-localisation in areas where opioid receptors are most dense. They probably explain the tissue-specific nature of proenkephalin post-translational processing observed (25, 62-64). In addition to mature enkephalins, other peptides are produced, one of which is a stable proenkephalin peptide-119-159. This fragment is stable in plasma and cerebrospinal fluid for at least 48 hours at room temperature, and it this molecule to which a novel sandwich immunoassay has been developed (PENK) (65). This peptide fragment's levels in plasma/serum could serve as a surrogate measurement of systemic enkephalin synthesis, as proenkephalin is the predominant source of mature enkephalins. For the remainder of this review, PENK will refer to the measurement of proenkephalin-119-159 using this assay, and

proenkephalin will refer to the precursor of mature enkephalins which has not been processed intracellularly.

Proenkephalin is a prognostic marker in several diseases

Plasma PENK levels have been measured in a variety of prospective cohorts. In cerebrospinal fluid, PENK was found to be strongly positively correlated with N-protachykinin A, a surrogate for substance P. Substance P is one of several signalling molecules released in response to nociception and is both a neurotransmitter and neuromodulator (66, 67) but has a plethora of other effects. It is lower in both dementia and acute cerebral inflammation compared to healthy individuals (68). In a prospective cohort of patients undergoing routine cardiac surgery, PENK predicts acute kidney injury, with a similar predictive capability as baseline creatinine (69). In addition, in patients admitted to the emergency department for sepsis, PENK predicts acute kidney injury (70). A recent study evaluated the prognostic value of PENK levels in 1141 patients with acute myocardial infarction by using N-terminal pro–B-type natriuretic peptide (NT-proBNP) and Global Registry of Acute Coronary Events (GRACE) scores as comparators. Endpoints included major adverse events (composite of death, myocardial infarction and heart failure hospitalisation) and recurrent acute myocardial infarction at 2 years. The results showed that PENK levels reflected cardiorenal status post-acute myocardial infarction and had a role as a predictor of major adverse events such as death, recurrent acute myocardial infarction and heart failure. Cut-off values of PENK levels <48.3 pmol/l and >91 pmol/l was able to define low- and high-risk patients and improve risk prediction of GRACE scores. The major determinant of PENK levels was renal function, and there was a strong negative correlation between PENK and estimated glomerular filtration rate (eGFR) (71). Furthermore, in healthy individuals, higher PENK predicts the development of kidney disease in later life, and is positively associated with creatinine and cystatin C and negatively associated with eGFR (72).

Additionally, Schulz *et al.* identified a single nucleotide polymorphism on the locus encoding proenkephalin which was associated with increased PENK levels and predicting kidney disease, implying potential causality of proenkephalin in the development of future kidney disease although in-depth exploration will be require.

Other examples of PENK predicting poor outcome is found in ischaemic stroke, where higher PENK was related to stroke severity, functional disability and mortality (73). Interestingly in this study plasma creatinine was not found to be a determinant of PENK levels. The authors attribute the relation of PENK to prognosis with it being a marker of blood-brain barrier integrity, allowing the high levels of PENK in CSF (100 fold higher than plasma (65)) to leak into the circulation. At present, it is not clear where most of the circulating plasma PENK is from, although Denning *et al.* demonstrated that multiple non-neuronal tissues express preproenkephalin mRNA, enkephalins and associated δ-opioid receptor's, but are of highest density in the kidney (74). Finally, lower PENK levels have been found to predict the development of breast cancer (75). Markers of renal function were not reported in this publication; however PENK levels measured in that study could be in keeping with the OGF-OGFr axis hypotheses. In a diabetic cohort, PENK was not found to predict long-term mortality. However, like other studies, it found significant association of PENK with serum creatinine (76). Table 1 summarises the non-heart failure studies that have used PENK to provide prognostic information.

Author	Type of Study	Number of patients	Inclusion Criteria	Endpoints	HR, OR or AUC	Comments
Doehner *et al.* 2012	Prospective observational, single centre	189	Acute Stroke	Mortality, MACE, Rankin Score	Mortality: HR 4.52 (1.1-19) MACE: HR 6.65 (1.8-24.9)	PENK not associated with renal function
Ng *et al.* 2014	Prospective cohort, single centre	1141	Unselected acute myocardial infarction	Composite of death, re-infarction, heart failure hospitalisation	All events: HR 1.52 (1.19-1.94) Death/MI: HR 1.76 (1.34-2.3) Death/HF: HR 1.67 (1.24-2.25) Recurrent MI: HR 1.43 (1.07-1.91)	PENK related to eGFR, LVWMI, sex, BP, age
Shah *et al.* 2015	Post-hoc analysis, single centre	92	Undergoing cardiac surgery	Acute kidney injury	OR 23.8 (2-270)	PENK Strong correlation with creatinine

Marino *et al.* 2015	Observational retrospective, single centre	101	Consecutive attendances for suspected sepsis in ED	Acute kidney injury and mortality at 7 days	AUC for AKI = 0.815 AUC for 7 day mortality = 0.69	PENK inversely correlated with creatinine clearance
Van Hateren *et al.* 2015	Prospective observational, ZODIAC study	1157	Diabetic population	Cardiovascular Mortality	HR 0.49 (1-1.21) No added predictive value	PENK correlates with creatinine
Melander *et al.* 2015	a) Malmo Diet and Cancer Study and b)Malmo Preventive Project	a)1929 b)1569	Healthy population	Incidence of Breast Cancer	a)HR 0.72 (0.62-0.85) b)OR 0.63 (0.52-0.76)	PENK not compared with renal function. Lower PENK associated with increased breast cancer incidence.
Schulz *et al.* 2017	Prospective cohort, Swedish population study	2568	Healthy population	Chronic kidney disease	OR 1.51 (1.18-1.94)	PENK correlates with creatinine.

Table 1: Summary of non-heart failure studies using PENK to provide prognostic information.

Proenkephalin in heart failure

There have been very few studies so far which evaluate the role of PENK in cardiovascular diseases, especially in heart failure. Several main studies and roles of proenkephalin in cardiovascular diseases are described below.

Proenkephalin is a marker for risk stratification in stable minimally or asymptomatic ambulatory community-dwelling patients

PENK may have a useful role in classifying risk for stable heart failure patients. Arbit and his colleagues performed the first study in evaluating the prognostic role of PENK in stable ambulatory patients. 200 patients with ACC/AHA stages A and B heart failure were recruited in a 4 year prospective cohort study. The end point of cardiovascular-related hospital admission or death were assessed. The results indicated that PENK levels were higher in patients who had a higher serum creatinine and lower estimated glomerular filtration rate (eGFR), lower left ventricular ejection fraction (LVEF), hypertension and diabetes. After 3.5 years of follow up, the results showed that highest PENK tertile had a hazard ratio of 3.0 (95% confidence interval 1.4 to 6.7) compared to the lowest tertile (p <0.007) for the primary end point. However, this study had its limitations which was conducted in a single-centre with 98% of male patients and only patients with ACC/AHA stages A and B were included in the analysis (77).

Proenkephalin is a marker of prognosis in patients with heart failure

In light of the strong associations between PENK and renal function, Matsue *et al.* investigated, in a chronic heart failure cohort of patients, the association between PENK, glomerular function and tubular function. They found that PENK was strongly associated with glomerular function but not tubular function. The authors also investigated the link between PENK and clinical

outcomes in 1589 patients with acute heart failure who fulfilled the inclusion criteria for a drug trial (Rolofylline). PENK was higher in patients with both acute and chronic heart failure compared to normal subjects. Furthermore, PENK was higher in acute heart failure compared to chronic heart failure. In the acute heart failure group, PENK was able to predict death at 180 days, heart failure rehospitalisation at 60 days, and death or cardiovascular or renal rehospitalisation at day 60 in univariable analyses, but its predictive value was lost in a multivariable model when adjustments to the PROTECT prognostic model were made, which included age, history of heart failure hospitalisation, severity of peripheral oedema, systolic blood pressure, serum sodium, blood urea nitrogen, creatinine and albumin. Moreover, PENK was positively correlated with albuminuria in the chronic heart failure cohort (78). These findings reinforce that PENK may be a novel renal marker.

More recently, Ng and colleagues measured PENK in acute heart failure patients, in a registry-like cohort study. This was a multicentre cohort involving 1908 unselected patients presenting with acute heart failure in three European sites. The primary endpoint was 1-year all-cause mortality and secondary endpoints included in-hospital mortality, all-cause mortality or heart failure rehospitalisation within 1 year and in-hospital worsening renal function. Plasma PENK was strongly correlated with renal function (eGFR). The findings in this study suggest that PENK levels have additive value in providing modest accuracy to predict worsening renal function, when added to a model which includes a history of renal impairment, systolic blood pressure and plasma sodium. PENK was independently prognostic for worsening renal function and levels increased over time while renal function deteriorated. During follow up, PENK was a strong independent predictor of mortality and death and/or heart failure for both short-term (3-month) and longer-term (1-year) follow up. In addition, PENK levels independently predicted outcomes at 3 or 6 months and were independent predictors of in-hospital mortality, predominantly down-classifying risk in survivors when added to clinical scores; levels <133.3

pmol/l and >211.3 pmol/l detected low-risk and high-risk patients, respectively. These PENK levels can be of use in making clinical decisions and predicting cardiorenal syndrome which may allow selection of acute heart failure patients for intensified therapy settings or ruling out such care in low risk patients. Additionally, improved risk prediction could facilitate decision making on the frequency of monitoring of renal function and rate of up titration of heart failure therapies (79). Table 2 summarises the studies that have used PENK for prognosis in heart failure. Figure 1 summarises the role of proenkephalin in prognosis for patients with cardiovascular diseases.

Author	Type of study	Number of patients	Inclusion Criteria	Endpoint	HR (95% CI)	Comments
Arbit *et al.* (2016)	Prospective cohort, single centre	200	ACC/AHA stages A and B	Cardiovascular-related hospital admission/death	3.0 (1.4-6.7)	PENK correlates with serum creatinine, eGFR, LVEF, hypertension and diabetes
Matsue *et al.* (2016)	Retrospective study	1589	Acute heart failure	Death/heart failure rehospitalisation/cardiovascular or renal rehospitalisation	NA	PENK correlates with diabetes, creatinine, and BNP, RBF and GFR
Ng *et al.* (2017)	Observational multicentre cohort study	1908	Acute heart failure	1 year all-cause mortality/in-hospital mortality/heart failure	1.27 (1.10-1.45)	PENK correlates with hypertension,

				rehospitalisation/in-hospital worsening renal function		IHD, HF, and renal impairment.

Table 2: Summary of studies using PENK for prognosis in heart failure.

Discussion

The strong association between PENK and renal function requires exploration, especially in light of the independent predictive value of PENK for mortality in heart failure, in addition to traditional risk markers and even after adjusting for renal function. Opioid agonist administration causes profound changes in renal excretory function (80). δ-opioid agonism increases both urinary water and sodium excretion, but lower doses of δ-opioid agonism only increases renal excretion of water. The use of a non-peptide δ-opioid receptor agonist BW373U86 increases urine output without change to heart rate or blood pressure, an effect which is abolished by selective δ-opioid receptor antagonism. Like in the heart, these effects seem paired to sympathetic activation and innervation, because the diuretic effect was abolished in rats having undergone bilateral renal denervation (81), although it is not clear at present whether this is due to the loss of afferent or efferent innervation. Whilst other mechanisms contribute to water and salt homeostasis in heart failure, this link strengthens the likelihood for a direct proenkephalin-renal relationship.

Summary

The enkephalin system plays a significant role in cardiovascular diseases. Plasma PENK, a stable and likely surrogate for mature intracellular enkephalin synthesis, has given new insight into mechanisms involved in various related cardiovascular diseases as well as the importance of the cardiorenal axis in prognosis in heart failure. PENK could be just a surrogate for

glomerular filtration rate. Being a stable and small peptide fragment (~4.5KDa), it is likely that PENK is filtered by the kidneys and has been demonstrated to associate with glomerular function, and not tubular function. However, due to the high density of δ-opioid receptors in the kidney and proenkephalin, as well as the likely autocrine/paracrine nature of enkephalin signalling, enkephalins are likely to have a direct effect on kidneys, especially in heart failure. Sympathetic pathways could link the heart and kidneys in a feedback axis which involves the brain and adrenals, with the ultimate aim of increasing urine output, and increasing cardiac output in heart failure. The effect of opioid receptor stimulation in the heart on blood pressure and heart rate may be partially beneficial for reducing preload and afterload, but the reduction in myocardial contractility seems counterproductive, but may be cardioprotective overall. Whether any of these pathways can be exploited to improve outcome in heart failure will require further investigative work.

Abbreviations

AKI: acute kidney injury

eGFR: estimated glomerular filtration rate

HF: heart failure

IHD: ischemic heart disease

LVEF: lower left ventricular ejection fraction

PENK: proenkephalin

RBF: renal blood low

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