RESEARCH ARTICLE

CARDIOVASCULAR EFFECTS OF GHRELIN IN HEART FAILURE: A SYSTEMATIC REVIEW

Mahalaqua Nazli Khatib[1], Shilpa Gaidhane[2], Padam Simkhada[3], Abhay Gaidhane[4], Quazi Syed Zahiruddin[4]

[1] Department of Physiology, JN Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra, India
[2] Department of Medicine, JN Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra, India
[3] The University of Sheffield. Western Bank, Sheffield, UK
[4] Department of Community Medicine, JN Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra, India

Correspondence to: Zahiruddin Quazi Syed (zahirquazi@rediffmail.com)

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ABSTRACT

Background: Ghrelin effects on cardiovascular system are inconclusive at present.

Aims & Objective: To determine the effectiveness of ghrelin therapy on weight gain, hormonal and cardiovascular outcomes in chronic heart failure.

Materials and Methods: All publications describing controlled trials of ghrelin in animal models of heart failure were sought through electronic searches. Two authors independently assessed all potentially relevant trials according to the prespecified selection criteria with an emphasis on selecting RCTs, and non-randomised trials. Also a third reviewer did an independent review to settle any difference of opinion between the two primary reviewers.

Results: The literature searches identified 106 references that described 57 potentially relevant trials. Five trials met the inclusion criteria and were included in this review. Three studies were randomised and the others were non- randomised. All HF models were administered ghrelin subcutaneously and trial periods lasted for as less as two days and as long as 28 days. Reported outcomes included cardiac effects and haemodynamic effect. It has been observed that chronic subcutaneous administration of ghrelin in rats with CHF reduces the development of cardiac cachexia and improved LV dysfunction. BIM-28131 is superior to BIM-28125 and human ghrelin in weight gain and induces a balanced gain of fat and lean tissue.

Conclusion: Ghrelin may has important cardio-protective significance in physiological and pathophysiological conditions. Studies suggest that Ghrelin may serve as a novel therapeutic tool for the prevention and treatment of CHF. Administration of ghrelin may be a new therapeutic approach to the treatment of CHF.

Key Words: Ghrelin; Chronic Heart Failure; Haemodynamic Effects

Introduction

Heart failure is a clinical condition in which the heart is not able to pump adequate amount of blood to fulfil the metabolic demand. It can be caused by anatomical defects, functional defects, or an acute overload beyond its ability.[1] The life expectancy of the population is increasing and so also the number of heart failure population is also growing. For both patients and their care givers heart failure can be a financial burden and have adverse effects on their quality of life.[2]

Therapy for heart failure includes disease counselling, lifestyle modifications (Exercise training, rehabilitation programmes, diet modification; etc.), drug therapy and invasive procedures.[1] Several new drugs with positive cardiac effect are being investigated. Many trials are now headway on a gut hormone: Ghrelin with a potential beneficial effects on cardiac function Ghrelin, a 28-amino acid peptide with n-octanoylation at serine 3, was originally identified in 1999 by Kojima[3] in rat stomach. Ghrelin is a brain-gut peptide and an endogenous ligand for the growth hormone secretagogue hormone receptor (GHS-R).[3] GHS-Rs are present in the hypothalamus, heart, lung, pancreas, intestine, and adipose tissue.[3] The highest concentration of ghrelin is found in the X/A-like cells of the oxyntic glands in the gastric fundus and other organs like small intestine, lung, pancreas, colon, pituitary, breast, kidney, and ovary.[4] Because of its widespread distribution, ghrelin plays a pivotal role in a various physiological processes including orexigenic regulation, neurohormonal control, energy and metabolic homeostasis, cardiovascular, immunological and other functions.[5] Ghrelin diverse actions makes it an attractive therapeutic tool for numerous diseases.[6-8] Although ghrelin was initially associated with regulation of appetite, and improving body weight, the cardiovascular system has also been recognized as a potentially important target for its effects on heart failure models and exploratory human clinical studies.

Ghrelin receptors are also found in myocardium aorta, coronary artery and vein[5] suggesting that ghrelin could directly exert cardiovascular effects by growth hormone-independent mechanisms. Experimental and a limited

number of clinical studies suggest a therapeutic role for the peptide hormone in patients suffering from heart failure and cardiac cachexia.[6]

Though ghrelin protects the myocardium and has various heart benefits, the underlying mechanism of the cardio-protective effects is yet unclear. Studies have suggested that ghrelin and other growth hormone secretagogues lowers the peripheral resistance either by its direct action on the vessels and /or by regulating the sympathetic nervous activity.[9] Both in vivo and in vitro studies have reported that Ghrelin improves the contractility and exerts an anti-inflammatory effect on the heart. Clinical studies have reported that exogenous administration of ghrelin may improve left ventricular function, decrease muscle wasting, improve exercise capacity, increase myocardial contractility, dilate peripheral blood vessels, decrease peripheral vascular resistance, constrict coronary artery, improve endothelial function, inhibit myocardial cell apoptosis, inhibit sympathetic nerve activity and protect from myocardial infarction - induced heart failure in vivo.[10] So also, ghrelin may have other cardiovascular protective effects, including lowering of blood pressure, regulation of atherosclerosis, and protection from ischemia/ reperfusion injury as well as improving the prognosis of heart failure.[11,12] Importantly, ghrelin has been shown to improve cardiac function in patients suffering from end-stage chronic heart failure.[7] In vitro, ghrelin decreases inotropism and lusitropism.[13,14] Experimental evidence suggests that ghrelin may have direct metabolic effects through GH-independent mechanisms: orexigenic effects[15,16]; glucose and lipid metabolism, attenuation of fat utilization[17]; energy and metabolic homeostasis, neurohormonal control, and inhibition of sympathetic nerve activities[11,18]. Ghrelin therapy can in future become a new pharmacological tool for the prevention and treatment of cardiovascular diseases. Ghrelin seems to be beneficial for CHF. However, the exact ghrelin effects on cardiovascular system are inconclusive at present. Since there is no systematic review about ghrelin in the prevention and treatment of CHF, the effects (including benefits as well as harms) of ghrelin need to be reviewed systematically.

This study objective was to comprehensively review the studies on effectiveness of ghrelin therapy on cardiovascular outcomes in rat models of heart failure with the purpose of promoting further studies on the role of ghrelin on the cardiovascular system.

Materials and Methods

Types of Studies: Randomized controlled trials (RCT) and the non-randomized studies which evaluated the effects of ghrelin in experimental rat models of CHF were searched. Any form, any dose and any route of administration of ghrelin was acceptable for inclusion in the review. Studies published only in abstract forms or non-peer reviewed journals whereby no further or insufficient information can be procured from the authors were excluded.

Types of Animal Models: Experimental rat models of CHF irrespective of the strain. No criteria was applied for age and weight of the rats.

Types of Interventions: Studies were included in which experimental intervention was done with any ghrelin at any dose, any analogue and any route. The interventions could be administered as single agents, combination therapies and in fixed or stepped/ titrated doses. Interventions were: (i) Trials of ghrelin versus control for chronic heart failure; (ii) Trials of ghrelin versus placebo for chronic heart failure; (iii) Trials comparing the different doses of Ghrelin; (iv) Trials comparing the different doses of ghrelin. Other treatments such as dietary control and restriction of fluid intake or conventional drug therapy was acceptable if given to both treated and control groups.

Types of Outcome Measures: (i) Mortality; (ii) Hemodynamic effect; (iii) Cardiac parameters; (iv) Adverse event outcome measures: Any adverse events as a result of treatment.

Outcomes: To review the cardiac protective effects of ghrelin in rat models of heart failure.

Search Methods for Identification of Studies: *(i) Electronic Searches:* All publications describing controlled trials of ghrelin in animal models of heart failure were sought through electronic searches on the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE (1999 to June 2013), EMBASE (1999 to June 2013), CINAHL (1999 to June 2013), AMED (1999 to June 2013), and Digital Dissertations. Conference proceedings were searched on Web of Science: ISI Proceedings (1999 to May 2013). Studies were also searched in Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). The bibliographies of all papers were

searched for further trials. No restrictions regarding the language of publication were imposed. The search was focused on randomized and controlled trials, systematic reviews, meta-analyses and review papers published within 1999 -2013. To avoid missing of studies in the search strategy, consideration was given to the spelling of terms used in different countries. If any data was found insufficient, the authors were contacted through e-mail. *(ii) Searching Other Resources:* Book chapters were also scanned. Manufacturers of ghrelin preparations experts and authors on the subject were contacted through emails and asked to contribute published and unpublished material. Hand searches were conducted for journals, and conference proceedings.

Data Collection and Analysis: Two authors independently assessed all potentially relevant trials according to the prespecified selection criteria with an emphasis on selecting RCTs, and non-randomised trials. Reviewers were blinded to authors of the studies. The references identified by the electronic search strategy were screened by title and abstract to determine eligibility for inclusion in this systematic review and the studies that appeared irrelevant were discarded. Full text of potentially eligible studies were retrieved (and translated into English where required) and two reviewers then independently determined study eligibility using a standardized inclusion form. Any disagreement about the eligibility of study was resolved by discussion. Also a third reviewer did an independent review to settle any difference of opinion between the two primary reviewers.

Selection of Studies: Data extraction and management: Data extraction was done independently by the two investigators using a pre-defined data extraction form. Study authors were contacted to seek clarifications on issues of reporting or to obtain further outcome details. Data unavailable in the trial reports were sought by contacting the principal investigators. Disagreements amongst the reviewers were resolved by discussion. If required, a third reviewer was consulted to resolve the disagreements.

Results of the Search: Using our search strategy, we assessed 106 references that described 28 potentially relevant trials, including 1 unpublished study and 1 ongoing study. There were only three human clinical trials evaluating the role of ghrelin in patients with CHF. Full texts of 16 studies were sorted out to be included into the review. Based on the criteria for inclusion in review and risk of bias screening, 10 studies were excluded and 6 studies were included in the review.

Description of studies: Six trials[7,11,19-22] met the inclusion criteria and were included in this review. One study[19] published two trials in a single manuscript. Three trials[11,20,21] were carried out in China and one trial each in countries like Japan, New Zealand and Germany[7,19,22]. Sample size ranged from 24 to 57 rats with a total of 303 rats recruited in the six studies. Four studies were done on Sprague–Dawley rats and one study was done on Wistar rats. One study did not mention the strain of the rat. All the studies were done on adult male rats weighing between 200-340 grams and experimental model of heart failure was created either by ligation of the coronary artery or was induced by isoprenaline (ISO). The controls were subjected to sham operation of a thoracotomy and cardiac exposure without ligation of the coronary artery. All HF models were administered ghrelin subcutaneously and the trial periods lasted for as less as two days and as long as 28 days. The daily dose used in these trials varied between the trials. In all the trials, ghrelin was not used as an adjunct to conventional treatment for heart failure.

Review found deficient information about effect of ghrelin on mortality, morbidity and adverse effects of ghrelin needed in recommendation for adoption of this therapy in treating CHF. The characteristics of the included studies were as shown in Table 1.

Results

Mortality was reported in three studies (Table 2). In the study of Lin Chang; none of the rats in Control (C) group, Ghrelin (G) group and Isoprenaline + Ghrelin in high dose (ISO + GH) group died during the experimental period. 5 out of 11 rats (45 %) died in the Isoprenaline (ISO) group whereas only 2 out of 11m (18%) rats died in the Isopreline + Ghrelin low dose (ISO+GL). However the difference was not statistically significant (P>0.05, compared with ISO group) Administration of ghrelin in high dose decreased mortality significantly.

In Daryl's study[22], the mortality in the MI rats treated with saline (MI + Saline) was 50% (seven of 14 MI rats) while in those MI rats treated with ghrelin (MI + Ghrelin) was 25% (three of 12 rats) which was not statistically significant (P= 0.286) thereby suggesting that administration of ghrelin did not significantly decrease mortality. In Zhang's study[20], 2 of 11 rats in ISO group died, whereas no mortality was observed in the other groups.

Table-1: Characteristics of the included studies

Study	Lin Chang (2004)	Nagaya (2001)	Akashi (2009)	Akashi (2009)	Daryl (2012)	Zhang (2013)	Jian Ping Xu (2010)
Country	China	Japan	Germany	Germany	New Zealand	China	China
Sample Size	47	57	49	54	36	36	24
Trial Period	2 days	21 days	28 days	28 days	14 days		
Study Population							
Lin Chang (2004)	Male Sprague Dawley rats; Wt: 200-250 g; Age: 10 to 12 weeks						
Nagaya (2001)	Male Wistar rats; Wt: 200 to 240 g						
Akashi (2009)	Male Sprague–Dawley rats; Wt:215 - 235 g; (mean 226.4±1.0 g)						
Akashi (2009)	Male Sprague–Dawley rats; Wt: 215 - 235 g; (mean 228.4±1.0 g)						
Daryl (2012)	Male Sprague Dawley rats; Wt:~ 280–340 g; Age: 8 wk						
Zhang (2013)	Adult male Sprague-Dawley (SD) rats; Wt: 250±10 g Age:1–2 day old						
Jian Ping Xu (2010)	Male rats						
Method of Induction of CHF							
Lin Chang (2004)	Myocardial injury induced by isoproterenol (ISO)						
Nagaya (2001)	Ligation of the coronary artery						
Akashi (2009)	Ligation of the coronary artery						
Akashi (2009)	Ligation of the left coronary artery						
Daryl (2012)	Ligation of the coronary artery						
Zhang (2013)	Myocardial injury induced by isoproterenol (ISO)						
Jian Ping Xu (2010)	Myocardial injury induced by isoproterenol (ISO)						
Intervention Groups							
Lin Chang (2004)	5 treatment groups: (i) C group: (*n*=7); (ii) G group: (*n*=7); (iii) ISO group (*n*=11); (iv) ISO+GL group: (*n*=11); (v) ISO+GH group: (*n*=11)						
Nagaya (2001)	4 treatment groups: (A) 31 infarct rats: (i) Ghrelin (n=16); (ii) placebo (n=15); (B) 26 sham rats: (i) Ghrelin (n=13); (ii) placebo (n=13).						
Akashi (2009)	4 treatment groups: (i) Sham (n=15); (ii) Placebo (n=16); (iii) GL (n=17); (iv) GH (n=16)						
Akashi (2009)	4 treatment groups: (i) Sham (n=15); (ii) Placebo (n=18); (iii) GL (n=17); (iv) GH (n=19)						
Daryl (2012)	3 treatment groups: (i) Sham; (ii) MI + Saline; (iii) MI + ghrelin						
Zhang (2013)	4 treatment groups: (i) Control (n = 9); (ii) ISO (n = 11); (iii) ISO + G (n = 9); (iv) ISO + metformin (n = 7)						
Jian Ping Xu (2010)	4 treatment groups (n = 6 each): (i) Control group; (ii) ISO group; (iii) GL (iv) GH						
Placebo/Control							
Lin Chang (2004)	C group: (n=7), 0.9 % NaCl (bid, sc).						
Nagaya (2001)	Sham operation of a thoracotomy and cardiac exposure without ligation of the coronary artery.						
Akashi (2009)	Sham operation of a thoracotomy and cardiac exposure without ligation of the coronary artery.						
Akashi (2009)	Sham operation of a thoracotomy and cardiac exposure without ligation of the coronary artery.						
Daryl (2012)	Saline (0.3 ml = MI+Saline) within 30 min of the infarct procedure.						
Dose & Route of Administration							
Lin Chang (2004)	(i) C group: 0.9 % NaCl (bid).; (ii) G group: Ghrelin of 10 nmol•kg-1•d-1(bid); (iii) ISO group: ISO of 40 mg•kg-1•d-1(bid); (iv) ISO+GL group: ISO+ ghrelin of 1 nmol•kg-1•d-1 (bid); (v) ISO+GH group: ISO+ ghrelin of 10 nmol•kg-1•d-1 (bid). Subcutaneously, BID						
Nagaya (2001)	100 µg/kg BID or saline in both CHF and sham-operated rats. Subcutaneously, BID						
Akashi (2009)	(i) Sham; (ii) Placebo; (iii) GL: 50 nmole/kg/d; (iv) GH:100 nmole/kg/d. Subcutaneously via osmotic mini-pumps						
Akashi (2009)	(i) Sham; (ii) Placebo; (iii) GL: 50 nmole/kg/d; (iv) GH:100 nmole/kg/d. Subcutaneously, TID						
Daryl (2012)	One bolus dose of 150 µg/kg ghrelin within 30 min of the infarct procedure. Subcutaneously, One bolus dose						
Zhang (2013)	(i) Control: saline (2 mL/kg/day, od) for 2 days; (ii) ISO: ISO (20 mg/kg/day, od) for 2 days; (iii) ISO plus ghrelin: Ghrelin (10−8 mol/kg/day, bd); (iv) ISO plus metformin: metformin (250 mg/kg/day, bd). Subcutaneously						
Jian Ping Xu (2010)	(i) Control group: sc saline (2 ml/kg) twice a day for 20 days; (ii) ISO group: ISO by 20,10, and 5 mg/kg/day for the first 3 days, then 3 mg/kg/day for the next 7 day; (iii) GL: ISO as in ISO group. Then ghrelin, sc 20 µg/kg/day for 10 days; (iv) GH: Same doses of ISO and in the same way as the ISO group. Then ghrelin, sc 100 µg/kg/day for 10 days. Subcutaneously						
Outcome Variables							
Lin Chang (2004)	Mortality, HR, MAP, LV dP/dtmax, LV dP/dtmin, LVEDP						
Nagaya (2001)	HR, MAP, SVR, mean RAP, CO, SV, LV dP/dtmax, LV dP/dtmin, LVEDP, diastolic thickness of non-infarcted posterior valve, LVDD, LVFS, shortening velocity.						
Daryl (2012)	HR, MAP, SVR, SV, EF, LV dP/dtmax, LV dP/dtmin, LVEDP, LVESP						

C group: control group; G group: Ghrelin alone group; ISO group: Isoproterenol (ISO) alone group; ISO+GL group: ISO + Low dosage of ghrelin treated group; ISO+GH group: ISO + High dosage of ghrelin treated group; HR : Heart rate; MAP: mean arterial pressure; LVEDP: Left ventricular end diastolic pressure; LVESP: Left ventricular end systolic pressure; LVDP: Left ventricular diastolic pressure; SVR: systemic vascular resistance; RAP: right atrial pressure; CO: cardiac output; SV: stroke volume; LVDD: left ventricular diastolic dimension; LVFS: LV fractional shortening; EF: ejection fraction

Table-2: Mortality in rat model of CHF

Study	Lin Chang (2004)	Nagaya (2001)	Akashi (2009)	Akashi (2009)	Daryl (2012)	Zhang (2013)	Jian Ping Xu (2010)
Mortality	(i) C group: 0% (0/7); (ii) G group: 0% (0/7); (iii) ISO group: 45 % (5/ 11); (iv) ISO+GL group: 18 % (2/11) (P> 0.05, compared with ISO group); ISO+GH group: 0 % (0/11). (P<0.05)	Not mentioned	Not mentioned	Not mentioned	(i) MI + Saline: 50% (7/14); (ii) MI + Ghrelin: 25% (3/12). (P = 0.286)	(i) Control: 0% (0/9); (ii) ISO: 18.18% (2/11); (iii) ISO + G: 0% (0/9); (iv) ISO + metformin: 0% (0/ 7)	Not mentioned

Table-3: Effect on haemodynamic functions	
Heart Rate (HR)	
Lin Chang (2004)	(i) Control: 387±17; (ii) G H: 394±11; (iii) ISO: 422±6 (P<0.05); (iv) ISO+GL: 422±17; (v) ISO+GH: 401±9
Nagaya (2001)	Lower in CHF rats treated with ghrelin than those given placebo; P=NS. P=NS in each group
Akashi (2009)	-
Akashi (2009)	(i) Sham: 319.9±6.5 (p<0.05); (ii) Placebo: 309.0±5.9 (p<0.05); (iii) GL: 326.2±4.9;(iv) GH: 318.3±5.6
Daryl (2012)	(i) Sham: 383 ± 13; (ii) MI + Saline: 387 ± 15; (iii) MI + Ghrelin: 383 ± 14. P=NS
Zhang (2013)	(i) Control: 394±13; (ii) ISO:429± 9(p<0.05); (iii) ISO+G: 419±6
Jian Ping Xu (2010)	-
Mean arterial pressure (MAP) (mmHg)	
Lin Chang (2004)	(i) Control: 82±4; (ii) GH: 84±4; (iii) ISO: 82±5; (iv) ISO+GL: 80±7; (v) ISO+GH: 82±5. P=NS between various groups
Nagaya (2001)	Lower in CHF rats treated with ghrelin than those given placebo; P=NS. Decreased in both sham-operated rats (-8 mm Hg,P<0.05) and CHF rats (-7 mm Hg, P<0.05).
Akashi (2009)	(i) Sham : 112.0 ± 3.6; (ii) Placebo: 101.1 ± 2.3; (iii) GL: 103.3 ± 2.7; (iv) GH:99.5 ± 2.3
Akashi (2009)	-
Daryl (2012)	No significant difference in mean ABP between all groups of rats (mean ABP range 85–91 mm Hg).
Zhang (2013)	(i) Control: 89±3; (ii) ISO:90±5; (iii) ISO+G:89±4
Jian Ping Xu (2010)	-
Systemic vascular resistance (SVR) (dynes/s/cm5)	
Nagaya (2001)	Significantly lower in CHF rats treated with ghrelin than in those given placebo. Ghrelin decreased SVR in sham, CHF (-12%, -13%, , P<0.05, respectively).
Akashi (2009)	(i) Sham : 0.41 ± 0.03; (ii) Placebo: 0.52 ± 0.03; (iii) GL: 0.55 ± 0.03; (iv) GH: 0.53 ± 0.02
Akashi (2009)	-
Mean right atrial pressure	
Nagaya (2001)	Lower in CHF rats treated with ghrelin than those given placebo;P=NS
Cardiac output (ml/min)	
Nagaya (2001)	Significantly higher in CHF rats treated with ghrelin than in those given placebo
Akashi (2009)	-
Akashi (2009)	(i) Sham: 149.0±11.8; (ii) Placebo: 94.8±6.0; (iii) GL: 96.6±6.2; (iv) GH: 99.3±6.1
Daryl (2012)	(i) Sham : 56.2 ± 1.5 ml/min; (ii) MI + Saline : 96 36.8 ± 2.6 ml/min. Sig different from sham rats (P < 0.01); (iii) MI + Ghrelin: 48.8±4 ml/min. Sig difference between MI + Saline and MI + Ghrelin rats (P < 0.05)
Stroke volume	
Nagaya (2001)	Significantly higher in CHF rats treated with ghrelin than in those given placebo
Daryl (2012)	(i) Sham :148 ± 7µl ,P=NS; (ii) MI+Saline : 96 ± 8µl. Sig different from sham rats (P < 0.01); (iii) MI+Ghrelin:126 ± 6. Sig difference between MI+Saline and MI+Ghrelin rats (P < 0.05)
EF (%)	
Akashi (2009)	(i) Sham : 80.1 ± 2.3; (ii) Placebo: 32.0 ± 2.7; (iii) GL: 31.1 ± 2.3; (iv) GH: 29.5 ± 1.9
Akashi (2009)	(i) Sham: 63.3±1.1(p<0.05); (ii) Placebo: 29.9±1.9; (iii) GL: 29.0±2.2; (iv) GH: 28.9±1.7
Jian Ping Xu (2010)	(i) Controls: 66.72±8.05; (ii) ISO: 55.16±8.98 (P < 0.05); (iii) ISO+ GL: 84.77±5.26 (P < 0.01 versus ISO group); (iv) ISO + GL: 85.87±5.36 (P < 0.01 versus ISO group)
LVEDV (ml)	
Akashi (2009)	(i) Sham : 1.06±0.08; (ii) Placebo: 2.61±0.11; (iii) GL: 2.50±0.12; (iv) GH: 2.59±0.17
Akashi (2009)	(i) Sham: 0.53±0.02; (ii) Placebo: 0.86±0.04(p<0.05); (iii) GL: 0.87±0.04(p<0.01); (iv) GH: 0.86±0.03
Jian Ping Xu (2010)	(in µl). (i) Controls: 302.75±88.19; (ii) ISO: 466.46±128.24 (P < 0.05); (iii) ISO+ GL: 160.53±53.60 (P < 0.01 versus ISO group); (iv) ISO + GL: 164.72±28.47(P < 0.01 versus ISO group)
LVESV (ml)	
Akashi (2009)	(i) Sham : 0.28±0.07; (ii) Placebo: 1.79±0.10; (iii) GL: 1.72±0.09; (iv) GH: 1.84±0.13
Akashi (2009)	(i) Sham: 0.19±0.01; (ii) Placebo: 0.61±0.04 (p<0.05); (iii) GL: 0.63±0.04 (p≤0.001); (iv) GH: 0.61±0.03
Systolic volume (ml)	
Akashi (2009)	(i) Sham : 0.86±0.05; (ii) Placebo: 0.83±0.07; (iii) GL: 0.78±0.07; (iv) GH: 0.75±0.07
Akashi (2009)	(i) Sham: 0.33±0.01; (ii) Placebo: 0.24±0.01; (iii) GL: 0.23±0.01; (iv) GH: 0.24±0.01
LV dP/dtmax (mm Hg/msec)	
Lin Chang (2004)	(i) Control: 3381±172; (ii) G H: 3197±282; (iii) ISO: 1761±183. P<0.05; (iv) ISO+GL: 3664±266. P<0.01 vs ISO group; (v) ISO+GH: 4038±166. P<0.01 vs ISO group
Nagaya (2001)	Significantly higher in CHF rats treated with ghrelin than in those given placebo. P=NS in each group
Akashi (2009)	-
Akashi (2009)	(i) Sham : 1466.4 ± 49.9; (ii) Placebo: 1331.3 ± 54.5; (iii) GL: 1339.5 ± 42.5; (iv) GH: 1273.9 ± 43.3
Daryl (2012)	(i) Sham: 11.3 ±0.9; (ii) MI + Saline : 7.4±0.7 Significantly different from sham rats (P=0.01); (iii) MI + Ghrelin: 9.4±0.7
Zhang (2013)	**+LVdp/dtmax:** (i) Control: 6794±114.3; (ii) ISO:5469±259.2(P < 0.01 vs. Con); (iii) ISO+G:2.2±0.6(P < 0.01 vs. ISO) **-LVdp/dtmax:** (i) Control: 4753±181; (ii) ISO:3501±268(P < 0.01 vs. Con); (iii) ISO+G:4358±271(P < 0.01 vs. ISO)
LV dP/dtmin (mm Hg/sec)	
Lin Chang (2004)	(i) Control: 2808±192; (ii) G H: 3197±282; (iii) ISO: 1750±179b; (iv) ISO+GL: 2741±327. P<0.01 vs ISO group; (v) ISO+GH: 2657±231. P<0.01 vs ISO group
Nagaya (2001)	Significantly lower in CHF rats given ghrelin
Akashi (2009)	(i) Sham : 1066.5 ± 38.3; (ii) Placebo: 907.2 ± 41.1; (iii) GL: 928.7 ± 35.2; (iv) GH: 926.5 ± 31.5
Akashi (2009)	-
Daryl (2012)	(i) Sham: -7.6±0.8; (ii) MI + Saline : -5.4±0.5 Significantly different from sham rats (P< 0.05); (iii) MI + Ghrelin: - 5.8±0.2
LV end-diastolic pressure (mmHg)	
Lin Chang (2004)	(i) Control: 6±2; (ii) G H: 4±2; (iii) ISO: 24±6. P<0.01 vs control group; (iv) ISO+GL: 2±1.P<0.01 vs ISO group; (v) ISO+GH: 4±1. P<0.01 vs ISO group

Table-3: Effect on haemodynamic functions	
Nagaya (2001)	Significantly lower in CHF rats given ghrelin.
Zhang (2013)	(i) Control: 2.1±0.8; (ii) ISO:8.5±1.8(P < 0.01 vs. Con); (iii) ISO+G:2.2±0.6(P < 0.01 vs. ISO)
Daryl (2012)	(i) Sham: 4.07 ± 1.61; (ii) MI + Saline: 4.07 ± 1.61; (iii) MI + Ghrelin : 3.12 ± 1.17. Significant difference between MI+Saline and MI+Ghrelin rats (P< 0.05; one way ANOVA)
LVESP (mmHg)	
Zhang (2013)	(i) Control: 124.1±2.8; (ii) ISO:117.5±2.1(P < 0.05); (iii) ISO+G:125.1±3.9(P < 0.05)
Thickness of noninfarcted posterior wall (mm)	
Nagaya (2001)	Increased in both CHF and sham rats T/t with ghrelin.
Akashi (2009)	(i) Sham : 1.76 ± 0.09; (ii) Placebo: 1.48 ± 0.09; (iii) GL: 1.56 ± 0.04; (iv) GH: 1.53 ± 0.08
Akashi (2009)	(i) Sham : 1.69 ± 0.08; (ii) Placebo: 1.55 ± 0.08; (iii) GL: 1.46 ± 0.07 (p<0.05 vs. Sham and 100 nmol/kg/d); (iv) GH: 1.67 ± 0.07
LV diastolic dimension (mm)	
Nagaya (2001)	Decreased in CHF rats T/t with ghrelin and increased in those given placebo.
Akashi (2009)	(i) Sham : 7.82±0.21; (ii) Placebo:10.89±0.18; (iii) GL: 10.69±0.19; (iv) GH: 10.82±0.28
Akashi (2009)	(i) Sham: 8.60±0.20; (ii) Placebo:10.81±0.24(p≤0.001); (iii) GL:10.79±0.20(p<0.01); (iv) GH:11.14±0.21(p<0.01)
LV fractional shortening (%)	
Nagaya (2001)	Increased significantly in CHF rats treated with ghrelin, although it tended to decrease in CHF rats given placebo (19±1% versus 17±1%, P<0.05). NS altered by each dose of ghrelin (99±3% for 1pmol/mL, 97±17% for 10 pmol/mL, and 91±15% for 100 pmol/mL), suggesting that ghrelin has no direct inotropic effects.
Akashi (2009)	(i) Sham : 44.8±2.1; (ii) Placebo:13.5±1.3; (iii) GL: 13.0±1.1; (iv) GH: 11.5±1.1
Akashi (2009)	(i) Sham: 39.1±1.1(p<0.05); (ii) Placebo: 15.5±1.0; (iii) GL: 14.4±1.2; (iv) GH: 14.7±1.0
Jian Ping Xu (2010)	(i) Controls: 40.11±3.04; (ii) ISO: 30.86±5.84(P < 0.05); (iii) ISO+ GL: 55.47±6.14(P < 0.01 vs ISO group); (iv) ISO + GL: 56.62±6.32(P < 0.01 vs ISO group)
Shortening velocity	
Nagaya (2001)	In ghrelin-treated CHF rats was significantly increased compared with that in CHF rats given placebo (278±14 versus 213±10 μm/s, P<0.001).
LV diastolic wall stress (kdyne/cm2)	
Nagaya (2001)	LV wall stresses in diastole were significantly lower in CHF rats T/t with ghrelin than those given placebo.
Akashi (2009)	(i) Sham : 8.5±1.9; (ii) Placebo: 45.7±5.2; (iii) GL: 46.1±7.2; (iv) GH: 40.1±3.2
Akashi (2009)	(i) Sham: -2.0±0.7; (ii) Placebo: 10.2±3.3; (iii) GL: 2.4±3.3; (iv) GH: 4.2±2.9
LV systolic wall stress (kdyne/cm2)	
Nagaya (2001)	LV wall stresses in systole were significantly lower in CHF rats T/t with ghrelin than those given placebo.
Akashi (2009)	(i) Sham : 22.9±2.7; (ii) Placebo: 120.9±10.9; (iii) GL: 129.7±8.9; (iv) GH: 114.0±7.7
Akashi (2009)	(i) Sham: 57.9±4.3; (ii) Placebo: 138.3±8.0; (iii) GL: 135.4±8.7; (iv) GH: 114.1±4.3

Cardiac and Hemodynamic Parameters: Various studies demonstrating the cardiac and hemodynamic effect of ghrelin on rat models of heart failure were compared and presented in table 3.

Heart Rate: In Lin's study[11] and Zhang's[20] study, ISO significantly increased HR as compared to the control group (P<0.05 vs control group in both the studies) and ghrelin did not significantly ameliorate tachycardia induced by ISO (P>0.05). In Nagaya's study[7], heart rate was lower in CHF rats treated with ghrelin than those given placebo (P=NS). However, the difference was insignificant. Daryl's study also showed similar insignificant difference in HR between all groups of rats.

MAP: In majority of the studies, there was an insignificant difference in MAP between control and ghrelin group and also between low dose and high dose of Ghrelin.[7.11,12] In Zhang's study[20], There was no difference in the MAP between the Control (C) group, Isoprenaline (ISO) group and Isoprenaline + ghrelin (ISO+G) group.

Systemic Vascular Resistance, Mean Right Atrial Pressure, Cardiac Output and Stroke Volume: In Nagaya's study[7], CHF rats treated with Ghrelin showed significant lowering of SVR than those treated with placebo. Ghrelin also decreased SVR in sham, CHF (-12%, -13%, P<0.05, respectively).In Akashi's study[19], systemic vascular resistance did not show any significant differences between infarct groups (all p values < 0.2). MRAP was insignificantly lower in CHF rats treated with ghrelin than those given placebo.[7] CHF rats treated with Ghrelin showed a significant increase in CO and SV than those treated with placebo.[7] Similarly Daryl's study also found significant difference between MI+ Saline treated rats and MI+ Ghrelin treated rats (P < 0.05).

LVdp/dt max and LVdp/dt min: Lin's study showed that, ghrelin potentiated cardiac function in the rats treated with ISO.[11] The rat cardiac function was significantly inhibited by ISO injection. Ghrelin administration (10 nmol•kg-1•d-1, 2 d) alone did not affect the cardiac function in normal rats. However, treatment with ghrelin (1and 10 nmol•kg-1•d-1, 2 d) in ISO+GL and ISO+GH groups reversed the inhibitory effects of ISO on cardiac function. LVEDP and +/-LVdp/dt max values were increased in ISO+GL and ISO+GH groups as compared with those in ISO alone group and the difference was statistically significant (all P<0.01). In Nagaya's study, LVdp/dt max and LVdp/dt min were insignificantly higher and lower respectively in CHF rats with ghrelin than in those given placebo (P=NS in each

group). In Zhang's study, ISO treatment significantly decreased ±LVdp/dtmax (both P < 0.01) as compared with control treatment. However, pretreatment with ghrelin significantly augmented ±LVdp/dtmax (both P < 0.01) as compared with ISO treatment alone.

LV End-Diastolic Pressure (LVEDP): In studies by Lin et al, Nagaya et.al and Daryl et.al LVEDP was significantly decreased by ghrelin treatment. In Zhang's study, ISO treatment significantly increased LVEDP (P< 0.01) and LVESP (P < 0.05) as compared with control treatment. However, ISO plus ghrelin decreased LVEDP (P < 0.01) and augmented LVESP (P < 0.05),which suggests that pretreatment with ghrelin significantly ameliorates cardiac function inhibited by ISO, as compared with ISO treatment alone.

Left Ventricular Posterior Wall Thickness (LVPW), LV Diastolic Dimension, LV Fractional Shortening, and Shortening Velocity: In Nagaya's study, LVPW thickness was increased after ghrelin administration and might be the process of LV remodeling. However, in Akashi's study, ghrelin did not alter the thickness of LVPW. This may be a result of the anti-apoptotic actions of ghrelin on cardiomyocyte death. In Nagaya's study, LV diastolic dimension was decreased in CHF rats T/t with ghrelin and increased in those given placebo. In Akashi's study, there was an insignificant difference in LV diameters between ghrelin-treated animals and placebo rats.

Ejection Fraction (EF): In Akashi's study, administration of 50 nmole/kg/d of human ghrelin group (p= 0.076) decreased the EF which did not change after high dose of ghrelin

Discussion

Overall the included studies have shown that ghrelin has various cardiovascular effects, including inotropic action, vasodilatation, anti-apoptosis, and anti-inflammation etc. which suggest that ghrelin may maintain cardiovascular homeostasis.

Various other mechanisms by which ghrelin performs these cardio-protective actions have been proposed. It has been reported that ERS and ERS-induced apoptosis contributes to the pathogenesis of ischemic heart disease, cardiomyopathy[23,24] heart failure[23,25] and heart I/R injury[26,27] Ghrelin can alleviate rat myocardial injury and/or cardiomyocytes apoptosis induced by ischemia/reperfusion (I/R)[26,28], isoproterenol (ISO)[29,30]. It can improve cardiac function and haemodynamic in rats with heart failure induced by ISO[11,20,29] and prevent early left ventricular remodelling after myocardial infarction. Ghrelin ameliorates ERS-induced myocardial injury and apoptosis in rat by activating AMPK.[29] However, the mechanism by which ghrelin inhibits ERS is still unclear. It has been known that ghrelin could also activate AMPK in heart[29], but if this effect of ghrelin is mediated by activation of AMPK is not clear. However, this mechanism of protection of heart by ghrelin needs further research.

With the hemodynamic and anabolic effects of GH/ insulin-like growth factor (IGF-1), ghrelin may also play a role in maintaining the myocardial growth via activation of the GH/IGF-1 axis. Jian Xu suggest that administration of ghrelin can attenuate the myocardial metabolic disorders. In contrast to the other studies, Akashi's study found that the dose and route of administration did not alter the improvement in cardiac function.[19] He suggested that the use of human instead of rat ghrelin and rats of Sprague Dawley strain instead of Wister rats is unlikely the cause of the lack of cardiac effects.

Implications for Practice: Considering that there are amount of ghrelin receptor in cardiovascular system, ghrelin may has important cardio-protective significance in physiological and pathophysiological conditions. Exogenous administration with ghrelin may serve as a novel therapeutic strategy for a number of cardiovascular diseases.

Implications for Research: The underlying mechanisms governing the long-term effect of ghrelin are unknown. Whether an early single bolus dose of ghrelin can chronically enhance cardiac energy utilization is an area that warrants further research. Effect of ghrelin on heart urgently requires further research to identify the potential reflex, signalling, cellular, and/or molecular pathways involved. Ghrelin is a recently identified novel hormone and can be an effective pharmacological tool for improving cardiovascular outcomes and thus warrants further research.

Conclusion

Administration of ghrelin did not significantly decrease mortality but administration of ghrelin decreased mortality in rats treated with ISO which suggests that ghrelin could be an endogenous protective factor against myocardium damage. Subcutaneous administration of ghrelin improved LV dysfunction and attenuated the development of LV remodeling and cardiac cachexia in

rats with CHF. Except for a study by Akashi (2009), all the studies have demonstrated the cardioprotective effect of Ghrelin. Various mechanisms have been proposed for these effects. To confirm whether exogenous administration of ghrelin could be a new therapeutic approach to the treatment of CHF in humans; double-blind, randomized placebo controlled studies are the need of an hour.

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