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Research Article

The Effect of Glucagon-like Peptide-1 Receptor Agonist (GLP1RA) on Hypertensive Induced Heart Failure with Preserved Ejection Fraction and Hypertensive Cardiomyopathy

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ABSTRACT

Recent preclinical data suggest that Glucagon-like Peptide-1 Receptor Agonist (GLP1RA) possesses cardioprotective properties against the pathophysiology of Hypertension (HT). We sought to unravel the potential therapeutic application of GLP1RA in a clinically relevant large animal model of hypertensive Cardiomyopathy (hCMP). We used a combination of Angiotensin II (Ang II) and Deoxycorticosterone Acetate (DOCA) pellets to induce sustained HT status and establish hCMP in porcine model. Changes in cardiac echocardiography, invasive hemodynamic parameters, neurohumoral biomarkers and inflammation-related cytokines were investigated in 23 adult pigs, among which 6 were serving as control, 9 were induced with HT, and the remaining 8 were HT-induced with GLP1RA treatment. Eight weeks after the study initiated, HT pigs have developed sustained high Blood Pressure (BP) at both systole and diastole. Phenotype of hCMP has also become significant as impairment in systolic/diastolic function left ventricular remodeling and cardiac hypertrophy was determined by echocardiogram and invasive hemodynamics. Additionally, blood Norepinephrine (NE) content, venoarterial NE gradient and pro-inflammatory cytokines in HT pigs were increased. GLP1RA treatment halted the elevation in BP, left ventricular remodeling and cardiac hypertrophy development; preserved the left ventricular systolic/diastolic function; reduced the venoarterial NE gradient and decreased pro-inflammatory cytokine levels in the hCMP pigs at 18 weeks. Our results demonstrate that GLP1RA treatment has a remarkable effect effect on reducing blood pressure and inflammation, and improving left ventricular function, thus indicating its potential therapeutic value in hypertension-induced heart failure in a large animal model of hCMP.

Keywords: Hypertension; Glucagon-like peptide 1 receptor agonist; Heart failure; Biomarkers; Models; Animal

Abbreviations: GLP1RA: Glucagon-like Peptide-1 Receptor Agonist; DOCA: Deoxycorticosterone Acetate; hCMP: hypertensive Cardiomyopathy; HF: Heart Failure; HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction

INTRODUCTION

Influence of heredity based on twin studies

Heart Failure (HF) is a major health problem affecting more than23 million people worldwide [1]. At least half of all hospitalized patients for HF are represented with Heart Failure with preserved Ejection Fraction (HFpEF) which is associated with significant morbidity and premature mortality [1]. HFpEF differs from traditional HF by impaired systolic function or a reduced Ejection Fraction (HFrEF) having nearly normal systolic function with unaffected Ejection Fraction (EF) [2,3]. What features HFpEF is the impaired relaxation and increased diastolic stiffness which together gives rise to ultimate ventricular diastolic dysfunction [4,5]. With unaffected EF, HFpEF is therefore associated with a better long-term survival and required a different therapeutic approach from HFrEF [6]. However, better long-term survival leads to less research and clinical attention on HFpEF than HFrEF. Up-till-now, no existing pharmacological or device therapy has been shown to efficiently improve the clinical outcomes of HFpEF [7,8]. Current existing difficulty in the development of effective therapeutic strategies for HFpEF is the insufficiency of large animal model establishment in which the associated pathophysiology of HFpEF is simulated. Among the various risk factors leading to HFpEF, chronic hypertension is highly associated and can develop in affected patients up to 80% or more.

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Cardiomyopathy derived from HT or hypertensive Cardiomyopathy (hCMP) is believed to be major cause for diastolic dysfunction by impairing Left Ventricular (LV) diastolic relaxation and resulting in hypertensive LV morphological remodeling with cardiac hypertrophy under chronic high Blood Pressure (BP) burden [9-11]. Application of intravenous infusion of Angiotensin II (Ang II) and subcutaneous implantation of Deoxycorticosterone Acetate (DOCA) mechanistically causes vasoconstriction and water-sodium retention, which together increases the Total Peripheral Resistance (TPR) and intravascular volume. According to known relationship between BP, TPR and cardiacoutput both Ang II and DOCA are capable of elevating systematic BP [12]. Earlier research has documented the existence of regional variations in Sympathetic Nerve Activity (SNA) in small animals such as rats, which were induced with HT through the administration of either Ang II or DOCA combined with a high-salt diet [13,14]. Utilizing the manageable size of these small animal models, researchers have additionally identified and established a strong correlation between HT and the function of inflammation in HFpEF induced by HT [15,16]. However, the contribution of large animal models of HT with hCMP has been limited in the past few decades and the relationship between regional changes in SNA, systematic changes in inflammation, and the emergence of HT remains unclear in large animal models [17-21].

In our study, we have successfully established a large animal model of sustained HT and hCMP in adult pigs that could mimic the clinical phenotype of refractory HT. Our approach involves the administration of a combination of low-dose Angiotensin II (Ang II) and continuous infusion, along with low-dose Deoxycorticosterone Acetate (DOCA) that ensures a constant release. Using this porcine hCMP model, we have evaluated the potential therapeutic implications of a Glucagon-like Peptide-1 Receptor Agonist (GLP1RA) in managing HT-induced Heart Failure with preserved Ejection Fraction (HFpEF) and hCMP.

METHODOLOGY

Study protocol

Our study was conducted in three stages: Baseline, 8-week follow-up, and 18-week follow-up. A total of 23 female farm pigs, aged 9-12 months and weighing 35-45 kg, were included in our study. We induced accelerated hypertension with hypertensive cardiomyopathy in 17 animals by combining continuous infusion of Angiotensin II (Ang II) with subcutaneous implantation of DOCA pellets. The remaining six animals were used as controls. To induce hypertension, we implanted a commercially available drug infusion pump containing 120 mg of Ang II in 12 mL sterile isotonic saline subcutaneously into the ventral aspect of the animal's right neck. The pump was connected to an intravenous catheter inserted into the right internal jugular vein, delivering Ang II at a constant rate of 2.5 uL/hr. DOCA pellets were implanted subcutaneously on the left neck to achieve a release rate of 100 mg/kg over 90 days. All animals with developed hypertension at the 8-week follow-up underwent selective angiogram, and eight were randomly selected to receive the GLP1RA agent, Liraglutide. The telemetered device was implanted in a pocket inside the neck region of all 23 pigs, which was connected to an intra-arterial catheter inserted into the animal's right carotid artery. BP measurement was collected twice a week, echocardiographic assessments were done once-in-two-week, and invasive hemodynamic assessments were conducted three times at baseline, 8 and 18-week follow-up.

Our study protocol was approved by the local institutional ethics committee for animal research prior to the start of the experiment. All experimental procedures were strictly performed in accordance with United States National Institutes of Health- published the "Guide for the Care and Use of Laboratory Animals".

Online-only Data Supplement provides detailed study methods of the invasive hemodynamic, echocardiographic, biomarker and histological assessments.

Statistical analysis

We used the SPSS software (SPSS, Inc., Chicago, IL, USA) to perform statistical analyses, including expressing continuous variables as mean ± SEM and conducting various comparison tests. Serial changes in BP, echocardiographic, invasive hemodynamic parameters, and biomarkers at different time points between groups were compared using 2-way repeated ANOVA with Tukey test. Between 8 and 18-week follow-up, differences in BP, hemodynamic parameter, and IL-6 were compared using 1-way ANOVA with Kruskal-Wallis test. The comparison of immunochemical staining results between groups was established using Independent Student t test. Value of $P<0.05$ marked the significance in these statistical analyses.

Data and resource availability

The data generated, analyzed and supported the findings of this study are available from the corresponding author up on reasonable request.

RESULTS

Pressure data

There were no significant changes observed in the C group for systolic and diastolic blood pressure, LVESP, and LVEDP from baseline to 8 and 18-week follow-up ($P>0.05$) (Figure 1A-1D). However, following the Ang II infusion and DOCA pellets implantation, there was a successful elevation in systolic and diastolic blood pressure in the HT group and Tx group at the 8-week follow-up compared to the C group $P<0.05$ (Figures 1A and 1B). Interestingly, while systolic and diastolic blood pressure continued to increase in the HT group, there was a significant decrease observed in the Tx group at the 18-week follow-up compared to the HT group ($P<0.05$) (Figure 1A and 1B). LVESP and LVEDP also showed an increasing trend in both the HT group and Tx group at the 8-week follow-up and in the HT group alone at the 18-week follow-up compared to the baseline and C group; $P<0.05$ (Figure 1C,1D). However, these pressure indices were decreased again in the Tx group at the 18-week follow-up, and the significant changes compared with its baseline or C group were absent $P>0.05$ (Figures 1C and Figure 1D). Due to the reduction in both blood pressure and LV pressure in the Tx group, there was a significant decrease observed between the HT group and Tx group at the 18-week follow-up (Figure 1C,1D; $P<0.05$). The increase in systolic and diastolic blood pressure in the HT group indicated that the establishment of a HT animal model was successful, and the continuous elevation ensured sustained HT by the combination of Ang II infusion and DOCA pellets implantation. While there was an increase in pressure observed in terms of LV systole and diastole, all the pressure burdens loaded by HT were significantly relieved with GLP1RA treatment.

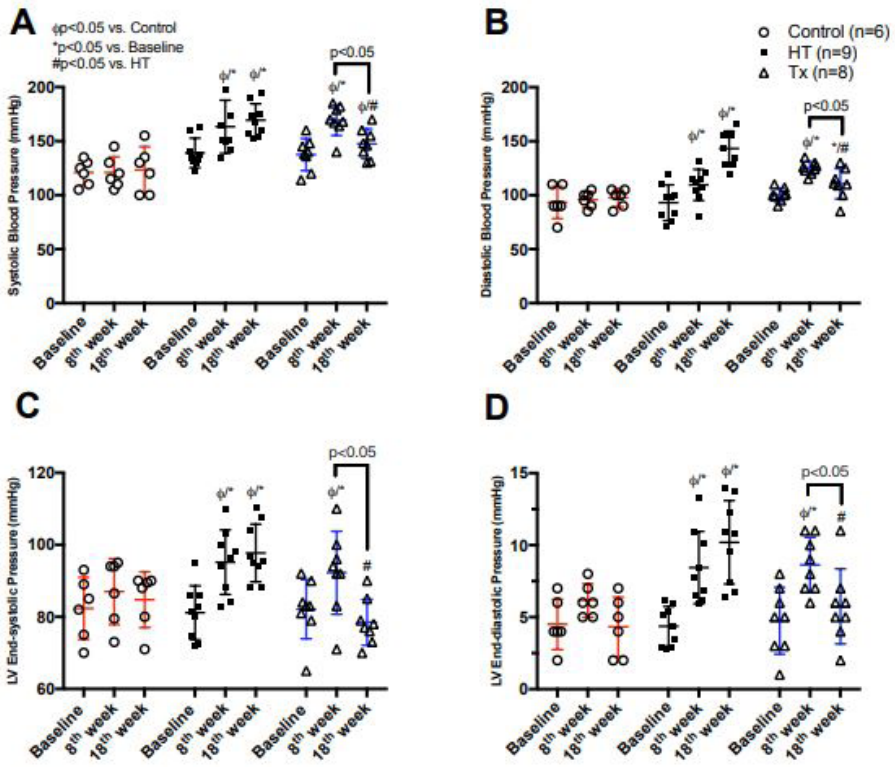

Figure 1: Hemodynamic parameters at baseline, 8-week and 18-week follow-up in control, hypertension and GLP1RA treatment groups. Serial changes to ambulatory blood pressure (A and B), left ventricular end-systolic pressure, and left ventricular end-diastolic pressure (C and D) in control (n=6), hypertension (n=9) and GLP1RA treatment. (n=8) groups. **Note:** (O) Control (n=6), (■) HT (n=9), (△) Tx (n=8); Ø: p<0.05 *vs.* Control, *p<0.05 *vs.* Baseline, #p<0.05 *vs.* HT.

Invasive hemodynamic data

Detailed invasive hemodynamic assessments were performed using LV pressure-volume loop analysis. LV systolic contractile function was assessed using several indicators including +dp/dtMAX, End-Systolic Pressure Volume Relationship (ESPVR), -dp/dtMAX, and End-Diastolic Pressure Volume Relationship (EDPVR). At both the 8 and 18 week follow-up points, the C group showed no significant changes in LV systolic contractile function compared to baseline; P>0.05 (Figures 2A-2D).

However, at the 18-week follow-up point, the HT group showed a significant decline in +dp/dtMAX and ESPVR compared to the 8-week follow-up point P<0.05 (Figures 2A and 2B), indicating a significant impairment in LV systolic function. In contrast, the Tx group did not show any significant changes in LV systolic function throughout the study course P>0.05 (Figures 2A and 2B).

There were no significant differences in the index of -dp/dtMAX in either the HT or Tx group at both the 8- and 18-week follow-up points (Figure 2C; P>0.05). However, a LV diastolic function impairment was observed in the HT group at the 8- and 18-week follow-up points compared to both the baseline and C group (Figure 2D; P<0.05), as evidenced by an increase in EDPVR. In contrast, the Tx group showed a significant decrease in EDPVR at the 18-week follow-up point compared to the HT group (Figure 2D; P<0.05).

Overall, the results of the invasive hemodynamic assessments indicated that developing HT is a key factor in diastolic dysfunction. However, treatment with GLP1RA may provide a therapeutic solution to HT-induced diastolic impairment.

Echocardiographic data

In pigs from C group, there were no serial changes in echocardiographic measurements of IVSd, LVPW thickness, LV mass index, LVd at both systole and diastole, or LVEF from baseline to 8- and 18-week follow-up (Figures 3A-3E; P>0.05). At 8-week follow212 up in HT group and Tx group as well as 18-week follow-up in HT group alone, IVSd, LVPW thickness and LV mass index were significantly increased compared with their baseline and C group (Figures 3A-3C; P<0.05). Differing from above, no significant changes were observed in LVPW thickness or LV mass index in Tx group at 18-week follow-up compared with C group (Figures 3B and 3C; P>0.05). Absence of significant changes were observed in LVd from all three group along the study course (Figure 3D; P>0.05). A decrease in the LVEF was detected in HT group when comparing itself at 8-week follow-up versus 18-week follow-up (Figure 3E; P<0.05), yet this significant reduction was not observed in C group and Tx group (Figure 3E; P>0.05), indicating that our animal models mimicked the phenotype of clinical HFpEF to a great extent. We additionally investigated LA volume and found no significant change in C group (Figure 3F; P>0.05), while HT group and Tx group at 8-week follow-up as well as HT group alone at 18-week follow-up preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission. This version posted in Biorxiv on February 12, 2023. The copyright holder for this exhibited statistically significant increase compared with its baseline and C group (Figure 3F; P<0.05). Results from echocardiographic assessment indicated that not only LV but LA has also been severely affected by sustained HT, and GLP1RA has the potential to attenuate the worsening in cardiac function to the contrary.

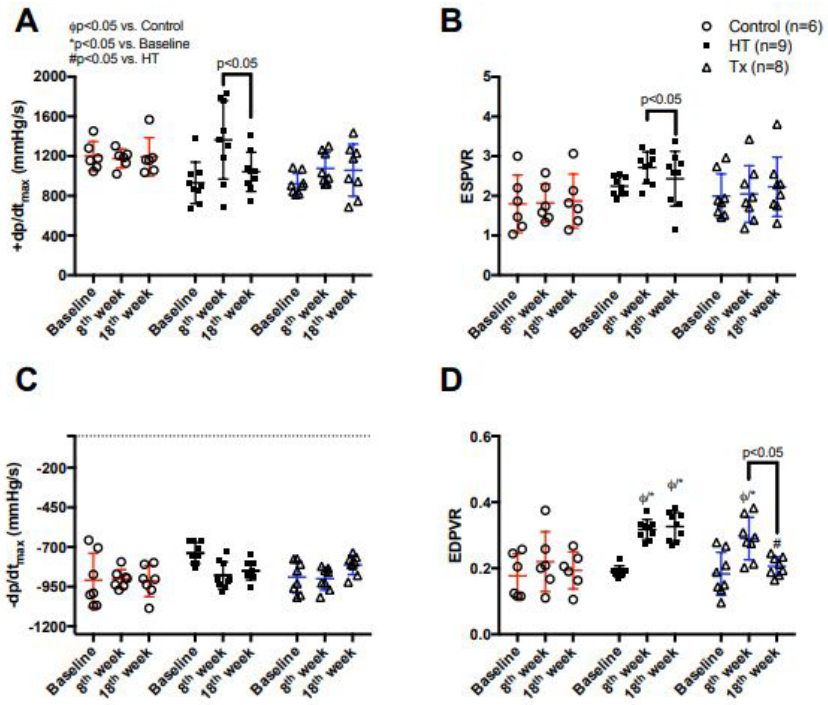

Figure 2: Pressure-volume loop assessment at baseline, 8-week and 18-week follow-up in control, hypertension and GLP1RA treatment groups. Serial changes to left ventricular systolic and diastolic function as determined by left ventricular +dp/dt (A), end-systolic pressure-volume relationship (B), left ventricular -dp/dt (C) and end-diastolic pressure-volume relationship, (D) in control (n=6), hypertension (n=9) and GLP1RA treatment (n=8) groups. **Note:** (O) Control (n=6), (■) HT (n=9), (△) Tx (n=8); Ø: p<0.05 *vs.*Control, *p<0.05 *vs.* Baseline, #p<0.05 *vs.* HT.

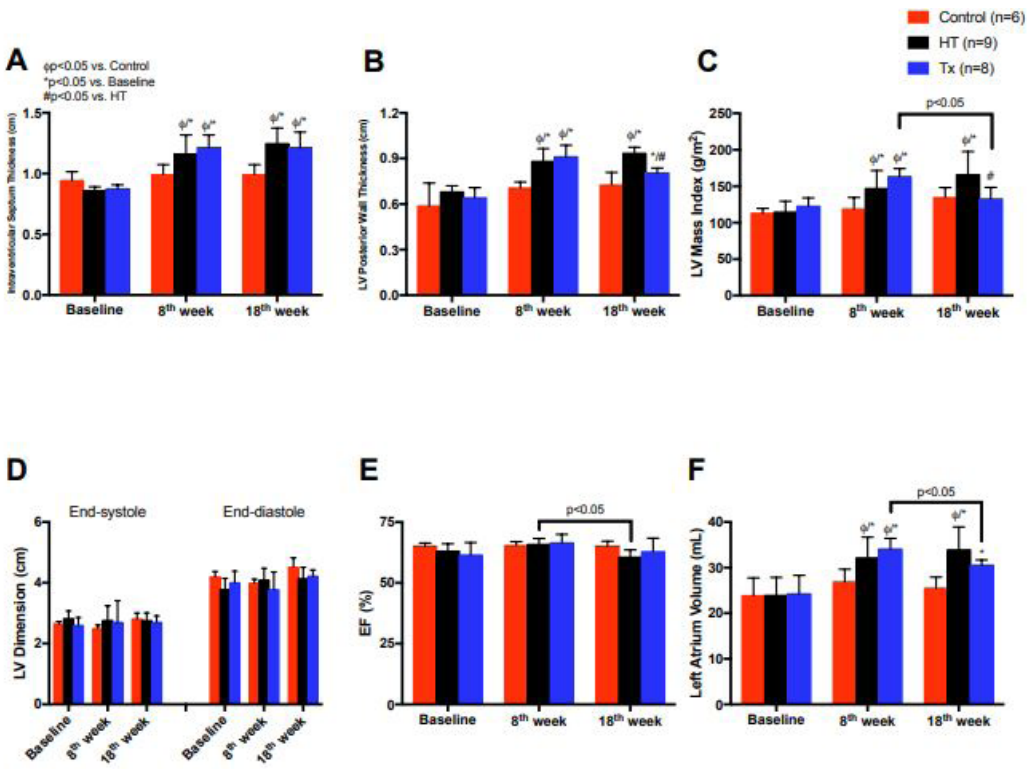

Figure 3: Echocardiographic parameters at baseline, 8-week and 18-week follow-up incontrol, hypertension and GLP1RA treatment groups. Serial changes to echocardiographic assessments of the left ventricle as determined by intraventricular septum thickness (A), left ventricular posterior wall thickness (B), left ventricular mass index (C), left ventricular dimension (D) and left ventricular ejection fraction (E), and serial changes to echocardiographic measurement of the left atrium as determined by left atrium volume (F) in control (n=6), hypertension (n=9) and GLP1RA treatment (n=8) groups. **Note:** (■) Control (n=6), (■) HT (n=9), (■) Tx (n=8); Ø: p<0.05 *vs.* Control, *p<0.05 *vs.* Baseline, #p<0.05 *vs.* HT.

General body condition and anatomical data

Since the animal models involved in our study were already adult pig model, The body length of the adult pig models used in our study did not differ significantly between the three groups over the course of the experiment (Figure 4A; P>0.05). However, despite being fed the same chow diet and the same amount, the body weight of the pigs varied. The HT group exhibited a continuous increase in body weight from baseline to 18-week follow-up, and the body weight at 18-week follow-up was significantly higher than that of the baseline and the C group (Figure 4B; P<0.05). The Tx group did not show a significant difference in body weight at 18-week follow-up compared to its baseline and the C group (Figure 4B; P>0.05), but a significant decrease was observed compared to the HT group (Figure 4B; P<0.05). Based on the body length data, the body weight-to-body length ratio (a parameter resembling body mass index in humans) was significantly increased in the HT group at 18-week follow-up compared to its baseline, the C group, and the Tx group (Figure 4C; P<0.05). Heart rate data were also collected, and both the HT group and the Tx group showed a significant increase in heart rate at 8- and 18-week follow-up compared to their baseline and the C group (Figure 4D; P<0.05).

The gross anatomy of the left ventricle showed a significant increase in heart weight at 18-week follow-up in the HT group compared to the C group (Figure 4E; P<0.05). However, such an increase was not observed between the C group and the Tx group (Figure 4E; P>0.05). The heart weight-to-body surface area ratio also showed the same increase between the HT group and the C group (Figure 4F; P<0.05). The general body condition and the heart anatomical results indicated that sustained HT caused an increase in body weight and heart weight, leading to hypertensive cardiac hypertrophy. Interestingly, GLP1RA treatment in animals with developed HT had the potential to attenuate abnormal body weight gain and reverse hypertrophy in the left ventricle. It is noteworthy that GLP1RA did not exhibit the expected capability of decreasing HT-induced heart rate elevation to baseline, which might be due to the direct activation of GLP1RA receptor located on the sino-atrial node, resulting in heart rate stimulation [22].

Histological and SNA data

Masson's trichrome staining revealed a dramatic increase in percentage area of fibrosis at the LV endocardium and mid-myocardium excised from animals sacrificed at 18- week follow-up in HT group compared with C group and Tx group (Figures 5A and 5B; P<0.05). However, no significant fibrotic increase was observed at LV epicardium among three groups (Figure 5C; P>0.05). As expected, Ang II and DOCA induced hypertensive cardiomyopathy exhibited extensive fibrosis in LV, suggesting the development of HF with reduced numbers of functional cardiomyocytes.

In HT group, both splanchnic and cardiac venoarterial NE gradient got significantly elevated at 18-week follow-up compared with its baseline and C group (Figure 5D and 5E; P<0.05).The increase in splanchnic gradient already became statistically significant at 8-week follow-up (Figure 5D; P<0.05) while the cardiac gradient at 8-week follow-up did not show any significance (Figure 5E; P>0.05). At 8-week follow-up, Tx group exhibited significantly higher splanchnic gradient compared with its baseline and C group (Figure 5D; P<0.05). However, when splanchnic gradient comparison established between Tx group and HT group at 18-week follow-up, Tx group showed a statistical decrease (Figure 5D; P<0.05). No obvious changes were observed in the cardiac gradient of Tx group at wither 8-week follow- up or 18-week follow-up compared with its baseline and C group (Figure 5E; P>0.05); this gradient in HT group significantly elevated compared with Tx group at 18-w eek follow-up (Figure 5E; P<0.05). In terms of tissue NE content measured from myocardium, kidney, duodenum, liver and spleen, spleen was the only organ detected to have a significantly higher tissue content in HT group compared with C group and Tx group (Figure 5F; P<0.05). NE, which is one of the important neurotransmitters in SNS, can indicate systemic and local SNA through its hormone level expressed in either venoarterial gradient or tissue [23]. During persistent hypertension, animals exhibited a continuous increase in venoarterial NE gradient as well as splenic tissue NE. Interestingly, GLP1RA treatment effectively repressed NE elevation, suggesting a SNA tune-down.

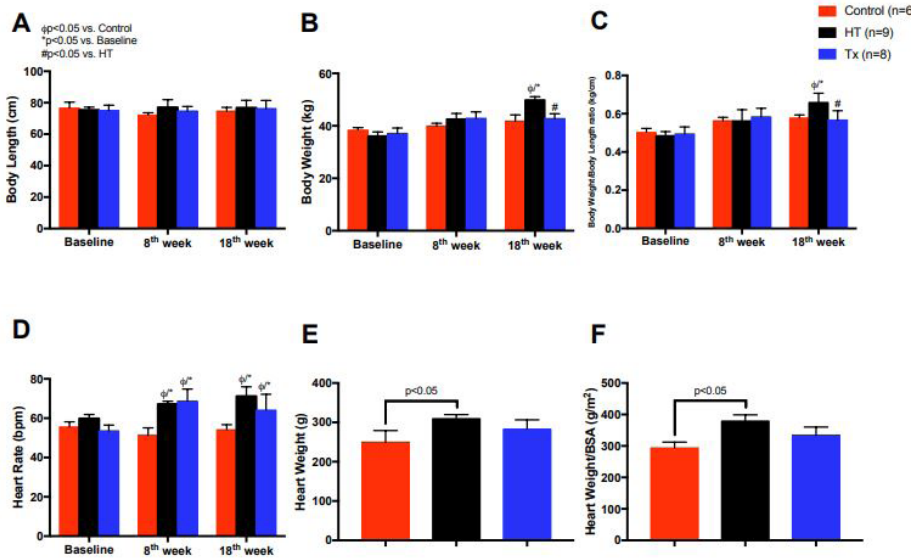

Figure 4: General body and heart condition, and heart rate at baseline, 8-week and 18- week follow-up in control, hypertension and GLP1RA treatment groups. Serial changes to body length (A), body weight (B), body weight/body length ratio (mimicking human body mass index; C) and heart rate (D) as well as heart weight (E) and heart weight/body surface area (F) in control (n=6), hypertension (n=9) and GLP1RA treatment (n=8) groups. **Note:** (■) Control (n=6), (■) HT (n=9), (■) Tx (n=8); Ø: p<0.05 *vs.* Control, *p<0.05 *vs.* Baseline, #p<0.05 *vs.* HT.

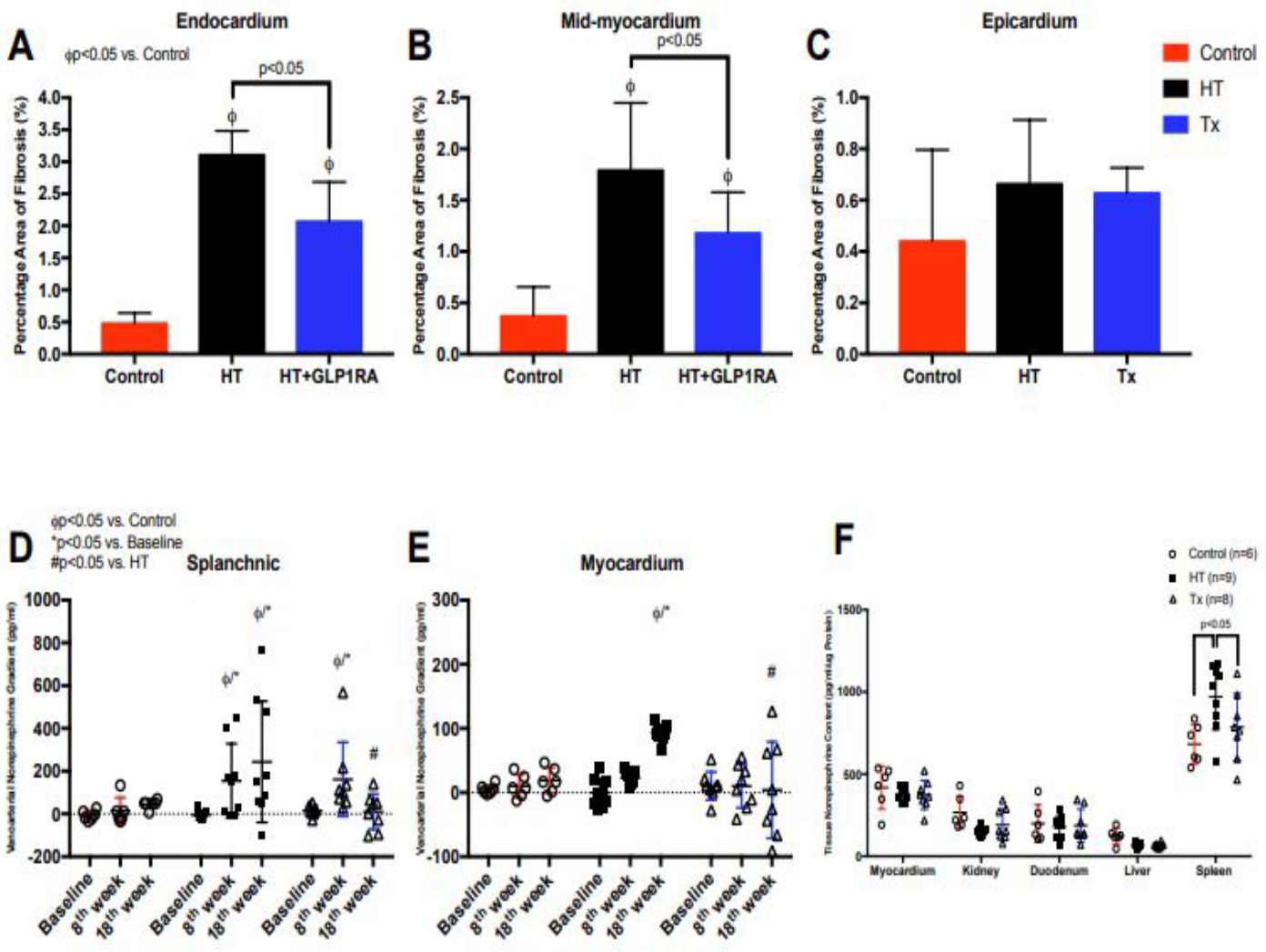

Figure 5: Myocardial fibrosis, venoarterial norepinephrine gradient and tissue norepinephrine content in control, hypertension and GLP1RA treatment groups. Percentage area of fibrosis in endocardium (A), mid-myocardium (B) and epicardium (C) as well as serial changes to venoarterial norepinephrine gradient over splanchnic organs and myocardium (D and E), and tissue norepinephrine content in various organs (F) in control (n=6), hypertension (n=9) and GLP1RA treatment (n=8) groups. **Note:** Ø: p<0.05 *vs.* Control, *p<0.05 *vs.* Baseline, #p<0.05 *vs.* HT.

Biomarkers and pro-Inflammatory cytokines data

At 18-week follow-up, the plasma Ang II, plasma NE, plasma BNP and plasma adrenaline in HT group was significantly elevated compared with its baseline and C group (Figures 6A-6C; P<0.05). In addition, the plasma Ang II was also significantly increased in HT group compared with Tx group (Figure 6A; P<0.05). In Tx group, the plasma Ang II at both 8- and 18-week follow-up, the plasma NE and plasma adrenaline at 18-week follow-up exhibited significantly higher than its baseline and C group (Figure 6A and 6C). Tx group also showed a significant increase in plasma BNP inter- group between itself at 8- and 18-week follow-up . There were no serial changes detected in the plasma renin or plasma creatinine between all three groups at each timepoint (Figure 6B).

At the 18-week follow-up, the Tx group showed a significant decrease in IL-6 levels measured from myocardium, kidney, and spleen when compared to the HT group and its 8-week follow-up (Figure 6D-6F; P<0.05), indicating the potential effectiveness of GLP1RA treatment in reducing pro-inflammatory cytokines. In addition, Masson's trichrome staining showed a decrease in fibrosis percentage in myocardial tissue. Conversely, the concentration of sICAM-1, a pro-fibrotic and pro-inflammatory molecule, was significantly higher in the myocardium, kidney, and spleen of pigs in the HT group at both 8- and 18-week follow-up periods, when compared to its baseline, C group, and Tx group.

The hypertensive pigs in our study had elevated levels of plasma Ang II, which led to an over-activation of the Renin-Angiotensin-Aldosterone System (RAAS) when initiated by Ang II infusion. This was accompanied by an increase in plasma BNP, which indicated deterioration in cardiac function. Additionally, under these hypertensive conditions, there was an increase in systemic SNA, as indicated by elevated levels of plasma NE and adrenaline. An over-activated SNS is known to enhance inflammation, which led to a significant increase in local inflammation in our hypertensive animals as expected [24]. Notably, treatment with a GLP1RA effectively reduced the elevation of SNA and inflammation induced by HT, thereby mitigating the local accumulation of pro-inflammatory cytokines and tuning down the RAAS and SNA.

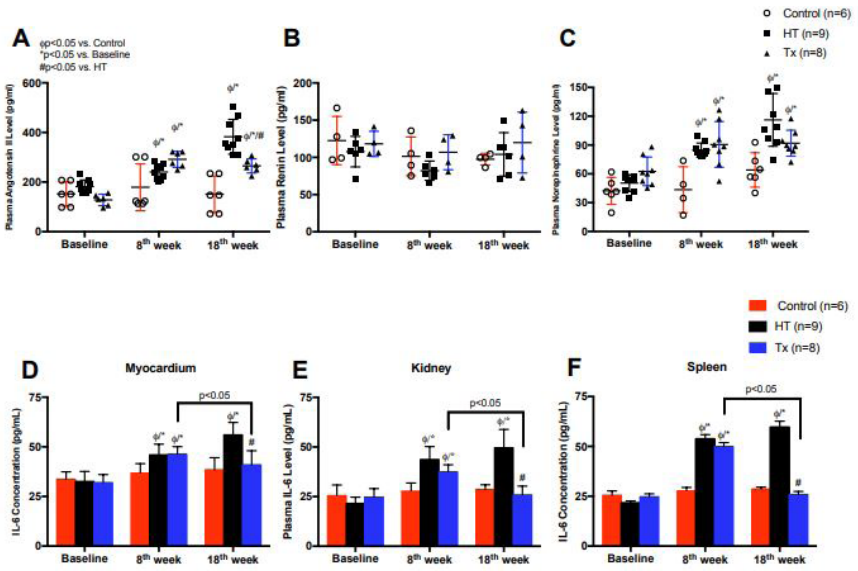

Figure 6: Plasma concentration of biomarkers and tissue concentration of IL-6 in control, hypertension and GLP1RA treatment groups. Serial changes to plasma Ang II (A), plasma renin (B) and plasma norepinephrine (C) as well as IL-6 tissue concentration in myocardium, kidney and spleen (D-F) in control (n=6), hypertension (n=9) and GLP1RA treatment (n=8) groups. **Note:** Ø: p<0.05 *vs.* Control, *p<0.05 *vs.* Baseline, #p<0.05 *vs.* HT.

DISCUSSION

Our study successfully established a large animal model of severe Hypertension (HT) and HT-induced hypertrophic Cardiomyopathy (hCMP) by using continuous infusion of Ang II and subcutaneous DOCA pellet implantation. After 8 weeks of HT induction, we observed progressive systolic and diastolic dysfunction, significant left ventricular remodeling, and cardiac hypertrophy, as determined by invasive hemodynamic assessment and speckle tracking strain imaging from echocardiography. We also identified significant local heterogeneity in Sympathetic Nervous System (SNS) activation in different organs by measuring the venoarterial NE gradients and tissue content of NE in HT animals. Our results showed a dramatic increase in NE gradient over the myocardium and splanchnic organs after HT induction compared to baseline levels, while tissue content of NE only increased significantly in the spleen. Treatment with a GLP1RA in HT pigs reduced SNS activity in the spleen, decreased the venoarterial gradient over the splanchnic organs, reduced levels of IL-6 and sICAM-1, and attenuated the elevation of blood pressure. In HT pigs with hCMP, treatment of GLP1RA also halted the increase in LVESP and LVEDP as well as the extent of LV remodeling and cardiac hypertrophy. Thus, upon GLP1RA implications both LV systolic and diastolic function were preserved. Although prior studies have successfully induced HT in animals using either a high dose of Ang II infusion or low dose DOCA pellets implantation with a high salt diet severe decrease in peripheral renin activity leading to different degrees of renal injury was observed as an adverse effect of such HT-induction administration [17,18,25]. Therefore, in our study we used a combination of low dose continuous Ang II infusion and subcutaneous DOCA pellets to induce sustained and severe elevation of BP.

This sustained BP increase in turn was established in a large animal model of HT with hCMP, which is one of the most major causes of HFpEF. Our animal models were featured with gradual rather than acute raise in plasma Ang II without serial changes in plasma renin. Such phenomenon shows high resemblance with the common human phenotype of refractory HT [26]. Interestingly, there was no significant change to renal function as measured by plasma creatinine and no evidence of local activation of RAAS over the myocardium or splanchnic organs in our animals.

Despite the absence of clinical signs of heart failure in our hypertensive animals, evidence from echocardiography and speckle tracking strain revealed a phenotype of progressive deterioration in left ventricular diastolic function and myocardial dysfunction, which are pathophysiological features of human hypertrophic cardiomyopathy (hCMP). Additionally, we detected other characteristics of hCMP, such as increased left atrial volume, significant left ventricular hypertrophy, and elevated myocardial fibrosis in our hypertensive animals.

A previous study investigated regional heterogeneity in the activation of Sympathetic Nervous Activity (SNA) during the pathogenesis of the disease in a hypertensive large animal model that closely resembles the human cardiovascular system [21]. Our results confirm these findings by observing a significant elevation of the venoarterial Norepinephrine (NE) gradient across the myocardium and splanchnic organs, as well as tissue content of NE in the spleen after inducing hypertension. These findings are similar to observations from clinical and experimental studies in Heart Failure with reduced Ejection Fraction (HFrEF) [23,27]. However, our animal models of hCMP with Heart Failure with preserved Ejection Fraction (HFpEF) are particularly notable for the prominent venoarterial NE gradient across the myocardium. Sympathetic nerves are believed to play an important role in modulating the immune response [28]. Evidence from this study suggests that short-term SNA activation mediates an anti-inflammatory reflect possibly via the regulation of macrophages located in its white pulp to control systemic inflammation. Nevertheless, the long-tern effects of SNA activation on immune response remain elusive. Prior experimental study confirms that the spleen is the key organ involving in linking the nervous system to the immune system [29]. This study has speculated that HT activates splenic SNA to prime an immune response that subsequentlycontributes

to the establishment and maintenance of elevated BP. Our results were consistentwith postulation as evidenced by a significant increased tissue content of splenic NE inhypertensive animals. In our hypertensive models administrated with GLP1RA treatment, asignificant decrease was observed in venoarterial NE gradient across both myocardium andsplanchnic organs, and the splenic tissue content of NE. This decrease was associated with areduced level of pro-inflammatory cytokines IL-6 and pro-inflammatory biomarker sICAM-Prior hypertensive large animal study involving splanchnic denervation illustrated similar result by a direct splanchnic denervation surgery which has effectively lowered BP, and NE expression both systemically and locally [21]. However, differing from their mechanism in which the reduction in SNA is the initial driving force of BP and inflammation decrease, GLP1RA treatment used in our study may yield the results in an opposite way. GLP1RA mimics the function of GLP-1 by activating downstream cellular pathways upon GLP-1 receptor activation [30]. Previous study using GLP1RA as a potential treatment to either obesity or obesity-derived chronic inflammation showed a significant increase in heart rate of the experimental models and this observation was also detected in our results. Interestingly, GLP1RA possesses the SNA activation property by directly stimulating the sino-atrial node to increase the heart rate [22,31]. Nonetheless, augmented SNA has the potential to exert negative effect on cardiovascular health so that GLP1RA treatment must have improved HT-induced hCMP or HFpEF against its SNA-favoring property in a different way [32]. As a typical treatment of type 2 diabetes, one of the direct functions of GLP1RA is to increase the insulin secretion and decrease the glucagon secretion [33]. Changes in these two hormones contribute to a decreased gastric emptying and hepatic production, and eventually they result in body weight loss. Since overweight or obesity is a common cause of chronic inflammation due to the overproduction of pro-inflammatory cytokines such as IL-6 from abnormal or excessive adipose tissue, reduced body weight can improve lipid profile, inflammation and decrease the burden on cardiac output [34]. In our results, hypertensive animals receiving GLP1RA treatment showed significant decrease in body weight/body length ratio, implying the weight loss effect of GLP1RA on these models. Accompanied with body weight loss, IL-6 and sICAM-1 as two major cardiovascular-associated pro-inflammatory cytokines exhibited dramatic reduction. Combining our results of both improved inflammation and halted BP increase, HT-induced SNA activation was eventually tuned down. Therefore, as the reduction in SNA is the initial driving force of BP and inflammation decrease in prior study alleviating the HT-derived inflammation might be the key target of GLP1RA treatment in approaching the same BP control and cardioprotective effect on hCMP and HFpEF [21].

Our study has certain limitations. Specifically, we did not observe any significant hemodynamic effects during a specific period after the administration of GLP1RA, leading to a lack of monitoring of the drug's acute effects. Furthermore, it should be noted that GLP1RA is primarily used in the treatment of type 2 diabetes, where insulin secretion and sensitivity are abnormal [35]. As such, the safety and efficacy of this drug for patients who are non-diabetic or non-obese, but admitted with HT-induced HFpEF alone, were not determined, despite the fact that many patients clinically admitted to type 2 diabetes have acquired a cardioprotective effect from GLP1RA [36]. Given that GLP1RA can directly stimulate the sino-atrial node and increase heart rate as an acute effect, we hypothesize that the use of this drug to treat HT and HT-induced HFpEF in patients admitted with severe congestive HF should be carefully considered.

CONCLUSION

As GLP1RA treatment halted the elevation in Blood Pressure, left ventricular remodeling and cardiac hypertrophy development; preserved the left ventricular systolic/diastolic function; reduced the venoarterial NE gradient and decreased pro-inflammatory cytokine levels in the hCMP pigs. This treatment has a remarkable effect on reducing blood pressure and inflammation, and improving left ventricular function, indicating its potential therapeutic value in hypertension-induced heart failure in a large animal model of hCMP.

PERSPECTIVES

Our study provides novel insight into the therapeutic potential of GLP1RA in HT-induced HF in a large animal model of hCMP. We also unravel the possible underlying mechanism of GLP1RA in BP control and cardio-protection against its SNA activation property.

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DUALITY OF INTEREST

The authors declare no competing conflicts.

AUTHOR'S CONTRIBUTIONS

H.S.H. conceived the project and designed the research. Z.Z.Y., L.S.Y., and Z.Z. performed the studies. S.S., L.W.H. and T.A. provided technical support. Z.Z.Y. and H.S.H. analyzed the data and wrote the manuscript.

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