

Combined effects of hydralazine and nitrate on serum biochemistry and left ventricular remodeling in chronic heart failure patients

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Abstract: To investigate the effects of hydralazine combined with nitrate on serum levels of Adropin and brain natriuretic peptide (BNP), left ventricular remodeling and prognosis in patients with chronic heart failure (CHF). 126 CHF patients were divided into control group (n=13, sodium nitroprusside) and combined treatment group (n=63, sodium nitroprusside + hydralazine). Serum Adropin and BNP levels and left ventricular mass index (LVMI) of patients before treatment and 10 days after treatment were recorded, so did patient's end-point events. It was found that compared with those before treatment, the serum levels of Adropin, BNP, and LVMI in combined group and control group after 10 days of treatment were lower ($P<0.05$). The end-point event rate in the combined group was 19.05% (12/63). The serum levels of Adropin, BNP, and LVMI in the combined group with end-point events were higher than those of patients without end-point events ($P<0.05$). Spearman correlation analysis showed that serum levels of Adropin and BNP were positively correlated with LVMI and the end-point events rate ($P<0.05$). To sum up, hydralazine combined with sodium nitroprusside treatment can effectively reduce serum Adropin and BNP levels, and the risk of left ventricular remodeling and poor prognosis in patients with CHF.

Keywords: Hydralazine; nitrate, chronic heart failure, adropin, brain natriuretic peptide, left ventricular remodeling.

INTRODUCTION

Heart failure, HF for short, refers to the failure of the heart's systolic and diastolic functions to fully discharge the venous return to the heart, resulting in blood stasis in the venous system and insufficient blood perfusion in the arterial system, which causes heart circulation disorders. Symptoms are generally caused by coronary heart disease, rheumatic heart disease, dilated cardiomyopathy, etc. (Sabry *et al.*, 2019). Chronic heart failure (CHF) is a persistent heart failure state that can stabilize, worsen, or decompensate. The clinical manifestations are dyspnea, fatigue, and fluid retention (Nakagawa *et al.*, 2019). Therefore, the goal of treating heart failure is not only to reduce the symptoms and improve the quality of life, but also to target the mechanism of myocardial remodeling, delay and prevent the development of myocardial remodeling, decrease the hospitalization rate and mortality of heart failure (Benic *et al.*, 2019). The commonly used therapeutic drugs include diuretics, angiotensin converting enzyme inhibitors and positive inotropic drugs, etc. Among them, nitrate is mainly used for patient's venous dilatation, and hydrazide is mainly used for patient's small artery dilation to reduce the heart load. Both these two are widely used clinically heart failure drugs (Mayama *et al.*, 2017).

Serum adropin is a secreted protein composed of 76 amino acids found in the liver gene of hypothalamic obese mice by Kumar *et al.* It is expressed in liver, heart, kidney, brain, pancreas and other tissues with various concentrations, and it is related to cardiovascular disease

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(Salvador *et al.*, 2016). Brain Natriuretic Peptide (BNP) is a peptide composed of 32 amino acid residues secreted by the heart. It belongs to the family of natriuretic peptides. It is widely distributed in brain, spinal cord, heart, lung, and other tissues. The effects of promoting sodium excretion, urination and vasodilation can counteract the vasodilator effect of the renin-angiotensin-aldosterone system. It can be activated in the cardiac dysfunction (Díez *et al.*, 2017). Clinical monitoring of hydrolyzed fragments of brain natriuretic peptides can reflect the severity of heart failure. The higher the level of brain natriuretic peptides, the more severe the heart failure, and the worse the prognosis (Kalkan *et al.*, 2018). The occurrence and development of heart failure is a progressive process, starting from the impairment of left ventricular function to the occurrence and subsequent deterioration of heart failure, which is manifested by progressive left ventricular enlargement and reduced function, so the key to preventing the heart failure is to prevent or reverse the left ventricular remodeling (Januzzi *et al.*, 2018; Radovanovic *et al.*, 2014; Lim *et al.*, 2019; Uriel *et al.*, 2018).

In summary, the use of nitrate and hydralazine as carotid artery dilators is a hot topic in currently clinical research, but the specific role of brain natriuretic peptide and left ventricular remodeling is still unclear. Based on this, the hydrazide and nitrate were selected in this study for the treatment of patients with CHF and the changes of serum adropin, BNP and left ventricular remodeling were explored in order to provide help for the clinical diagnosis and treatment of CHF.

MATERIALS AND METHODS

General information

126 patients with CHF admitted to our hospital from January 2016 to June 2019 were selected prospectively and continuously as the research objects. The study was approved by the Ethics Committee of the hospital (ethics committee approval No. 2020063-001) and each patient signed an informed consent to participate in the study. The inclusion criteria are as below: all were in line with the relevant diagnostic criteria in the 2014 *Chinese Heart Failure Prevention and Treatment Guidelines* (Dick and Epelman, 2016), all of which were treated for the first time, the gender is not required, the age was 18 to 80 years old, NYHA was in II to IV and the left ventricular ejection fraction was below 45%. The exclusion criteria were as below: patient having other disease affecting the cardiac function, BNP and adropin secretion, CHF and abnormal liver and kidney function caused by obvious organic disease of the heart, cerebrovascular disease, or being allergic to the drugs for treatment, and having the mental disorders, etc. The selected patients were randomly and prospectively divided into the combined group (n=63) and control group (n=63). The study met the ethical standards, and both groups of members signed the informed consents. The difference in baseline data of patients in the two groups was not statistically significant ($P>0.05$) and was comparable, as shown in table 1.

Treatment method

The control group was intervened with nitrate (sodium nitroprusside, manufacturer: Hunan Kelun Pharmaceutical Co., Ltd.; dosage form: injection; specification: 50mg; batch number: H20033674), the initial dose of intravenous infusion was $3\mu\text{g} / \text{min}$, and the dose was gradually increased until the diastolic pressure was controlled at 90~100 mmHg. The combined group was intervened with hydralazine based on the intervention of the control group (manufacturer: Guangdong Leiyunshang Pharmaceutical Co., Ltd.; dosage form: tablet; specification: 10mg* 14s; batch number: H44022996, usage: oral after meals, three times a day, 300mg/d in total). Both groups were treated continuously for 10 days.

Observation indicators and detection methods

Before the treatment and after 10 days of the treatment, 5mL of fasting venous blood was taken separately to detect serum Adropin and BNP levels. The blood samples were routinely centrifuged and refrigerated. Serum Adropin and BNP levels were detected by enzyme-linked immunosorbent assay (ELISA). The Swiss Tecan Infinite M1000 PRO multi-functional micro plate reader and the relevant kits provided by Shanghai Renjie Biotechnology Co., Ltd. were used and specific testing operations shall be accordance with the instructions of the relevant testing kits and the instruments' instructions. LVMI was examined by echocardiography before and after 10 days

of the treatment in both groups. The examination was performed by using the $\alpha 6$ Aloca color doppler (Japan ALOKA Co., Ltd.) with a frequency of 2MHz to 4MHz under the condition that the left chest was exposed fully and the breath was calmly. The left ventricular mass and the body surface area of each patient were calculated (male: $0.0057 \times \text{height} + 0.012 \times \text{weight} + 0.0082$; female: $0.0073 \times \text{height} + 0.0127 \times \text{weight} + 0.2106$), and the LVMI was calculated according to the equation "LVMI = left ventricular mass / body surface area". The combined group was followed up for at least 1 year by outpatient or telephone follow-up, and the incidence of end-point events (death, cardiovascular disease, and rehospitalization due to heart failure) was counted during the follow-up.

STATISTICAL ANALYSIS

The SPSS22.0 software was used for data entry and analysis. Measurement data was expressed as mean \pm standard deviation ($\bar{x} \pm s$), and count data was expressed as percentage (%). One-way ANOVA was used to analyze the serum Adropin, BNP levels, LVMI, and end-point event rates of patients in the combined group and the control group. The correlations between serum Adropin and BNP levels and end-point events were analyzed by Spearman. The sensitivity, specificity and accuracy of serum Adropin, BNP and the combination of these two items on the detection of end-point events were analyzed by ROC curve. $P<0.05$ means the difference had a statistical significance.

RESULTS

Comparison of serum Adropin and BNP levels and LVMI level of two groups

Compared with the conditions before treatment, the levels of serum Adropin and BNP and the LVMI level of patients in both the combined group and control group were lower 10 days after the treatment, and the levels of serum Adropin and BNP as well as LVMI of patients in the combined group were lower than those in the control group. The difference had a statistical significance ($P<0.05$). The details were shown in table 2.

Analysis on prognosis conditions in the combined group

During the follow-up of the combined group, there were 3 patients with death, 4 patients with cardiovascular disease, and 5 patients with rehospitalization due to the heart failure. There were 12 (3 + 4 + 5) patients had end-point event in total, and the incurrence rate was 19.05% (12/63).

Comparison of serum Adropin and BNP levels and the LVMI level of patients with different prognosis conditions in the combined group

Compared with the patient without the end-point event, serum Adropin and BNP levels and the LVMI level of

patients with the end-point events in the combined group were high averagedly and the difference had a statistical significance ($P < 0.05$). The details were shown in table 3.

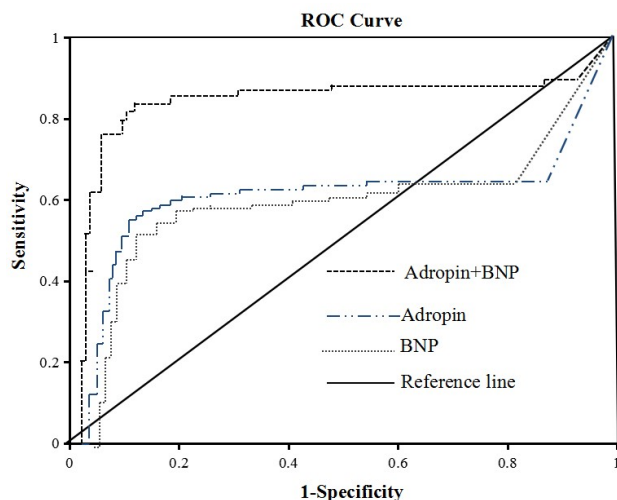


Fig. 1: ROC curve of predicating the occurrence of end-point- event by the serum Adropin and BNP levels in the combined group before the treatment

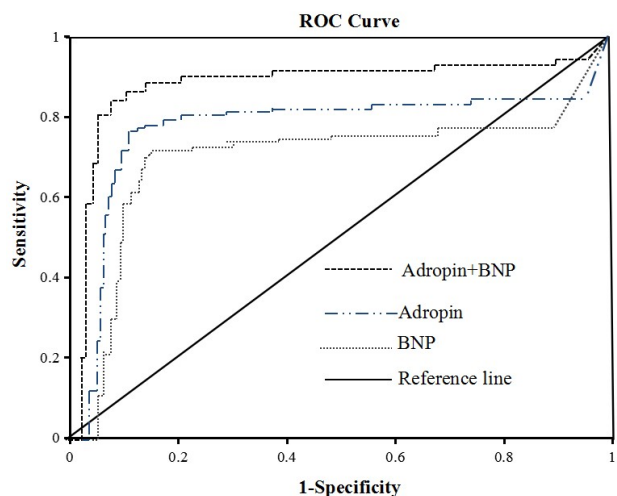


Fig. 2: ROC curve of predicating the occurrence of end-point- event by the serum Adropin and BNP levels in the combined group 10 days after the treatment

Analysis on relationship between serum Adropin and BNP levels and the LVMI level as well as the end-point event rate in the combined group

It was found by the Spearman correlation analysis that the serum Adropin and BNP levels and the LVMI level as well as the end-point event rate in the combined group had positive correlations (Adropin: $r=0.826, 0.875$; BNP: $r=0.798, 0.844, P < 0.05$).

Analysis on predication value of end-point event by the serum Adropin and BNP levels in the combined group

It was found by the ROC curve analysis that it had high sensitivity, specificity and accuracy in predicting

occurrence of end-point event by the serum Adropin and BNP levels in the combined group. The details were shown in table 4, fig. 1 and fig. 2.

DISCUSSION

CHF is a symptom of ventricular pumping and decreased filling function caused by a variety of reasons. Patients may have symptoms such as dyspnea, fatigue, and even ventricular remodeling in a severe case, leading to the occurrence of adverse prognosis conditions (Edelmann *et al.*, 2018; Tham *et al.*, 2015). In this study, it focuses on ventricular remodeling index LVMI and the prognosis indicators of death, cardiovascular disease, and rehospitalization due to heart failure. The results show that the LVMI indicators in patients with CHF are greatly higher, which can cause the ventricular remodeling, affecting the conditions and prognosis of patients, and more than one-fifth of patients after treatment have the adverse prognosis conditions. Improving the ventricular remodeling and prognosis status of the patients with CHF is a topic to be solved urgently (Dini *et al.*, 2011; D'Auria *et al.*, 2018; Motiwala *et al.*, 2014; Ky *et al.*, 2013).

The treatment of CHF is mainly based on the drug intervention. Nitrate can reduce the blood pressure, systemic circulation resistance, and left ventricular filling pressure, and improve the heart index to improve the condition of CHF (Ho *et al.*, 2016; Zhang *et al.*, 2019). Hydralazine can be used in the treatment of hypertension, congestive heart failure, and other treatments to achieve the effect of improving the condition by dilating smooth muscle, dilating arteries, and reducing the resistance of vascular resistance in other states (Ypenburg *et al.*, 2009). In this study, hydralazine and nitrate are combined to treat the patients with CHF, and the ventricular remodeling and prognosis indicators are observed. The results show that compared with treating with nitrate alone, combination of hydralazine and nitrate to treat the patients with CHF can reduce the risk of ventricular remodeling effectively to reduce the impact of the ventricular remodeling on the conditions and prognosis.

The occurrence and development of patients with CHF involve multiple pathological processes with changes of multiple serological indicators. As a quantitative marker of the heart failure, BNP may be abnormally elevated under the condition of ventricular dysfunction (Khanam *et al.*, 2017; Januzzi *et al.*, 2019). Adropin is a secreted protein and a regulating peptide of energy homeostasis. It can play a role of protecting the vascular endothelial and is closely related to various cardiovascular diseases. It plays the role of protection from the atherosclerosis, coronary heart disease, high blood pressure, and some other diseases. However, its level under the condition of heart failure is abnormally high and is related to the deterioration of cardiac function (Yosae *et al.*, 2016;

Table 1: Comparison of baseline data of patients in two groups

Group	Quantity	Gender (male/female)	Age	Body mass index (kg/m ²)
Combined	63	29/34	66.85±11.43	22.75±3.96
Control	63	26/37	67.48±15.24	22.62±3.18
<i>X²/t</i>		0.290	-0.262	0.203
<i>P</i>		0.590	0.794	0.839

Table 2: Comparison of serum Adropin and BNP levels and LVMI level of two groups

Time	Group	Quantity	Adropin (ng/mL)	BNP (pg/mL)	LVMI (g/m ²)
Before treatment	Combined	63	9.24±2.45	728.87±57.96	113.36±12.24
	Control	63	9.28±2.11	725.75±55.43	113.87±12.15
	<i>t</i>		-0.098	0.309	-0.235
	<i>P</i>		0.922	0.758	0.815
10 days after the treatment	Combined	63	4.87±1.68 ^a	349.96±32.69 ^a	95.54±9.78 ^a
	Control	63	6.16±1.27 ^b	426.68±51.14 ^b	102.27±11.76 ^b
	<i>t</i>		-4.862	-10.033	-3.492
	<i>P</i>		0.000	0.000	0.001

Note: compared with the conditions before treatment in the same group, ^a*P*<0.05, ^b*P*<0.05

Table 3: Comparison of serum Adropin and BNP levels and the LVMI level of patients with different prognosis conditions in the combined group

Time	End-point event	Quantity	Adropin (ng/mL)	BNP (pg/mL)	LVMI (g/m ²)
Before treatment	Yes	12	11.42±2.96	886.63±58.16	121.75±14.87
	No	51	7.68±1.78	703.44±42.43	108.42±10.92
	<i>t</i>		4.202	12.502	3.542
	<i>P</i>		0.001	0.000	0.001
10 days After the treatment	Yes	12	6.75±1.82	398.96±37.59	115.56±10.72
	No	51	4.02±1.05	325.44±32.18	88.69±8.92
	<i>t</i>		5.004	6.898	9.034
	<i>P</i>		0.000	0.000	0.000

Table 4: Analysis on predication value of end-point event by the serum Adropin and BNP levels in the combined group (%)

Time	Index	Critical value	Sensitivity	Specificity	Accuracy
Before treatment	Adropin	11.26ng/mL	58.33	88.24	82.54
	BNP	826.15pg/mL	58.33	82.35	77.78
	Adropin+BNP	11.41ng/mL+873.96pg/mL	83.33	88.24	87.30
10 days after treatment	Adropin	6.73ng/mL	75.00	92.16	88.89
	BNP	391.19pg/mL	66.67	86.27	82.54
	Adropin+BNP	6.59ng/mL+396.48pg/mL	91.67	94.12	93.65

Duan *et al.*, 2019). In this study, it also focuses on the levels of serum BNP and Adropin in patients with CHF. The results show that the levels of serum BNP and Adropin in patients with CHF increased, which is consistent with the results of previous studies. After a period of intervention, the levels of serum BNP and Adropin decreased gradually. Combined treatment of CHF with hydralazine and nitrate can reduce the levels of serum BNP and Adropin more quickly and effectively, and the levels of serum Adropin and BNP and LVMI in patients with end-point events were higher, which is different from the results of Naenni *et al.* (2019) that

hydralazine could independently lower the blood pressure without changing the heart remodeling and kidney damage in animal models. The reason for the analysis may be that the combined treatment of hydralazine and nitrate could improve the ventricular dysfunction of patients with CHF and reduce the blood pressure of the body, which is a common effect. It suggests that the levels of serum Adropin and BNP may be correlated to the level of LVMI and the end-point event. It is proved by further Spearman correlation analysis. Levels of serum Adropin and BNP are related to the end-point event, which may be used for the early assessment of its end-point event. The

further ROC curve analysis proves the application value of levels of serum Adropin and BNP in the evaluation of end-point events. After the treatment, the combined levels of these two items has high sensitivity, specificity, and accuracy to predict the occurrence of end-point events. Specially, when the level of serum Adropin is higher than 6.59ng/mL or the level of serum BNP is higher than 396.48 pg/mL after the treatment, it shall pay close attention to and intervene the occurrence of its end-point event in time to improve its conditions and prognosis.

CONCLUSION

In summary, hydralazine combined with nitrate CHF can reduce the risk of left ventricular remodeling and adverse prognosis effectively, while its levels of serum Adropin and BNP are closely related to the left ventricular remodeling and adverse prognosis, and the high levels of serum Adropin and BNP may indicate the risk of left ventricular remodeling and adverse prognosis, which requiring related intervention timely.

REFERENCES

- Benic GI, Eisner BM, Jung RE, Basler T, Schneider D and Hämmerle CHF (2019). Hard tissue changes after guided bone regeneration of peri-implant defects comparing block versus particulate bone substitutes: 6 month results of a randomized controlled clinical trial. *Clin. Oral Implants Res.*, **30**(10): 1016-1026.
- D'Auria F, Polito MV, Vitulano G, Ciccarelli M, De Rosa R, Gigantino A, Piscione F and Galasso G (2018). Predictors of left ventricular reverse remodeling in patients with chronic heart failure. *J. Cardiovasc. Med. (Hagerstown)*, **19**(8): 465-469.
- Dick SA and Epelman S (2016). Chronic heart failure and inflammation: What do we really know? *Circ. Res.*, **119**(1): 159-176.
- Díez J (2017). Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. *Eur. J. Heart Fail.*, **19**(2): 167-176.
- Dini FL, Capozza P, Donati F, Simioniuc A, Corciu AI, Fontanive P, Pieroni A, Di Bello V and Marzilli M (2011). Patterns of left ventricular remodeling in chronic heart failure: prevalence and prognostic implications. *Am. Heart J.*, **161**(6): 1088-1095.
- Duan J, Chen Z, Wu Y, Zhu B, Yang L and Yang C (2019). Metabolic remodeling induced by mitokines in heart failure. *Aging (Albany NY)*, **11**(17): 7307-7327.
- Edelmann F, Knosalla C, Mörike K, Muth C, Prien P and Störk S (2018). Chronic Heart Failure. *Dtsch. Arztebl. Int.*, **115**(8): 124-130.
- Ho EC, Parker JD, Austin PC, Tu JV, Wang X and Lee DS (2016). Impact of nitrate use on survival in acute heart failure: A propensity-matched analysis. *J. Am. Heart Assoc.*, **5**(2): e002531.
- Januzzi JL, Butler J, Fombu E, Maisel A, McCague K, Piña IL, Prescott MF, Riebman JB and Solomon S (2018). Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF). *Am Heart J.*, **199**: 130-136.
- Januzzi JL Jr, Ahmad T, Mulder H, Coles A, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Mark DB, Piña IL, Passmore G, Whellan DJ, Cooper LS, Leifer ES, Desvigne-Nickens P, Felker GM and O'Connor CM (2019). Natriuretic Peptide Response and Outcomes in Chronic Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol.*, **74**(9): 1205-1217.
- Kalkan AK, Cakmak HA, Erturk M, Kalkan KE, Uzun F, Tasbulak O, Diker VO, Aydin S and Celik A (2018). Adropin and irisin in patients with cardiac cachexia. *Arq Bras Cardiol.*, **111**(1): 39-47.
- Khanam SS, Son JW, Lee JW, Youn YJ, Yoon J, Lee SH, Kim JY, Ahn SG, Ahn MS and Yoo BS (2017). Prognostic value of short-term follow-up BNP in hospitalized patients with heart failure. *BMC Cardiovasc. Disord.*, **17**(1): 215.
- Ky B, French B, May Khan A, Plappert T, Wang A, Chirinos JA, Fang JC, Sweitzer NK, Borlaug BA, Kass DA, St John Sutton M and Cappola TP (2013). Ventricular-arterial coupling, remodeling, and prognosis in chronic heart failure. *J Am Coll Cardiol.*, **62**(13):1165-1172.
- Lim HC, Wiedemeier DB, Hämmerle CHF and Thoma DS (2019). The amount of keratinized mucosa may not influence peri-implant health in compliant patients: A retrospective 5-year analysis. *J. Clin. Periodontol.*, **46**(3): 354-362.
- Mayama M, Yoshihara M, Uno K, Tano S, Takeda T, Ukai M, Kishigami Y and Oguchi H (2017). Factors influencing brain natriuretic peptide levels in healthy pregnant women. *Int. J. Cardiol.*, **228**: 749-753.
- Motiwala SR, Szymonifka J, Belcher A, Weiner RB, Baggish AL, Gaggin HK, Bhardwaj A and Januzzi JL Jr (2014). Measurement of novel biomarkers to predict chronic heart failure outcomes and left ventricular remodeling. *J Cardiovasc Transl Res.*, **7**(2): 250-261.
- Naenni N, Lim HC, Papageorgiou SN and Hämmerle CHF (2019). Efficacy of lateral bone augmentation prior to implant placement: A systematic review and meta-analysis. *J. Clin. Periodontol.*, **46**(Suppl 21): 287-306.
- Nakagawa Y, Nishikimi T and Kuwahara K (2019). Atrial and brain natriuretic peptides: Hormones secreted from the heart. *Peptides.*, **111**: 18-25.
- Radovanovic S, Savic-Radojevic A, Pekmezovic T, Markovic O, Memon L, Jelic S, Simic D, Radic T, Pljesa-Ercegovac M and Simic T (2014). Uric acid and gamma-glutamyl transferase activity are associated with left ventricular remodeling indices in patients with

- chronic heart failure. *Rev. Esp. Cardiol. (Engl Ed).*, **67**(8): 632-642.
- Sabry DA, Cordeiro SL, Ferreira Silva CH, Cunha Farias EH, Sasaki GL, Nader HB and Oliveira Rocha HA (2019). Pharmacological prospection and structural characterization of two purified sulfated and pyruvylated homogalactans from green algae *Codium isthmocladum*. *Carbohydr Polym.*, **222**: 115010.
- Salvador AM, Nevers T, Velázquez F, Aronovitz M, Wang B, Abadía Molina A, Jaffe IZ, Karas RH, Blanton RM and Alcaide P (2016). Intercellular adhesion molecule 1 regulates left ventricular leukocyte infiltration, cardiac remodeling, and function in pressure overload-induced heart failure. *J. Am. Heart Assoc.*, **5**(3): e003126.
- Tham YK, Bernardo BC, Ooi JY, Weeks KL and McMullen JR (2015). Pathophysiology of cardiac hypertrophy and heart failure: Signaling pathways and novel therapeutic targets. *Arch. Toxicol.*, **89**(9): 1401-1438.
- Uriel N, Sayer G, Annamalai S, Kapur NK and Burkhoff D (2018). Mechanical unloading in heart failure. *J. Am. Coll. Cardiol.*, **72**(5): 569-580.
- Yosae S, Soltani S, Sekhavati E, Jazayeri S (2016). Adropin: A novel biomarker of heart disease: A systematic review article. *Iran J. Public Health*, **5**(12): 1568-1576.
- Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ and Bax JJ (2009). Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol.*, **53**(6):483-490.
- Zhang L, Tang F, Cai LP, Wang HL and Wang Z (2017). Research on the correlation of urine calcium integrin binding protein-1 and pro-BNP with ischemic heart failure. *Eur. Rev. Med. Pharmacol. Sci.*, **21**(18):4181-4185.