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Original Research

Effect of trimetazidine combined with perindopril on NT-proBNP level in rats with dilated cardiomyopathy

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Abstract: This experiment aimed to study the effect of trimetazidine combined with perindopril on NT-proBNP levels in rats with dilated cardiomyopathy (DCM). 40 SD rats were selected and 10 rats were randomly selected to continue to be fed as the blank group. The other 30 rats were injected with adriamycin to establish the DCM rat model. Then they were divided into 3 groups, namely control group (without any drug intervention), trimetazidine group (with trimetazidine single-agent intervention) and combination drug group (with trimetazidine combined with perindopril intervention), with 10 DCM rats in each group. After 4 weeks of intervention, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic diameter (LVESD) of rats were measured by echocardiography. The changes of plasma brain natriuretic peptide (BNP) level and n-terminal pro-brain natriuretic peptide (NT-proBNP) were detected by ELISA. RT-PCR was used to detect the regulation of angiotensin II type 1 receptor (AT1Rs) and lamin A mRNA expression in rat myocardium. After the intervention, the LVEF%, LVEDD and LVESD measured values of the rats in the combination drug group were significantly better than those in the trimetazidine group and the control group ($P< 0.05$). The BNP, NT-proBNP and AT1Rs levels of the rats in the combination drug group were significantly lower than those in the trimetazidine group and the control group. The difference was statistically significant ($p< 0.05$). The lamin A expression of the rats in the combination drug group was significantly higher than that in the trimetazidine group and the control group. The difference was statistically significant ($P< 0.05$). Compared with trimetazidine single-agent, trimetazidine combined with perindopril can significantly improve the cardiac function of rats with dilated cardiomyopathy, reduce the serum NT-proBNP level and improve the expression of AT1Rs and lamin A in rats.

Key words: Trimetazidine; Perindopril; Dilated cardiomyopathy rats; Serum NT-proBNP.

Introduction

DCM is a myocardial disease with reduced LVEF due to dysfunction of left ventricular dilation and systolic function (1). DCM is the most common cause of heart transplantation and one of the leading causes of death in western countries (2). One in 250 adults is ill (3). Generally, 40% of DCM patients are hereditary in the family. The prevalence rate of males is higher and the average age is higher than that of females (4). Studies have found that the survival rate of DCM patients is only about 40% in 5~10 years after onset (5). The extremely high family heritability causes great economic and health burden on families and society, so its diagnosis and effective treatment deserve social attention (5-10).

The etiology and pathogenesis of DCM are complex. Studies have found that more than 50 single-gene mutations are closely related to DCM. Lamin A mutation is one of the common causes of DCM. Lamin A is an intermediate filament protein existing in the nuclear membrane and nucleoplasm and is a fiber structure providing support for the nuclear membrane (11, 12). Lamin A mutation is characterized by atrioventricular conduction block, elevated serum creatine kinase level and skeletal muscle involvement in some cases. It also increased the risk of life-threatening ventricular arrhythmia (13), which has research significance. Echocardiography is currently the commonly used diagnostic method for DCM in clinical practice (14). LVEF is one of the important examination indexes. BNP and NT-proBNP, as cardiac biomarkers, are essential tools for clinicians, which are helpful to distinguish the causes of cardiac and non-cardiac dyspnea, as well as to facilitate prognosis and monitor therapeutic effects (15). The study found that the expression of BNP and NT-proBNP increased in DCM patients (16). BNP is believed to be beneficial to heart, vessel and kidney (17). The endogenous concentration of BNP can be increased by inhibiting neutral endopeptidase (NEP) (18). Since NEP also degrades AT1Rs, NEP inhibition must be joint with angiotensin-converting enzyme inhibitor (ACEI) (19). ACEI can improve left ventricular systolic and diastolic function, improve hemodynamics and significantly improve the prognosis of patients (20). Perindopril is a long-acting ACEI, which can prevent Ang I from converting to Ang II, reduce the effect of Ang II-mediated by ATR1s binding and significantly improve cardiac function (21). Combined with trimetazidine can restore autophagy and prevent cardiac apoptosis (22).

In this study, trimetazidine combined with perindo-

pril was used to treat DCM rats. Its effect on NT-proBNP level in rats was studied to provide an effective reference basis for clinical diagnosis and treatment.

Materials and Methods

Experimental animals

40 healthy adult male SD rats were purchased from the Shanghai branch of Beijing Weitonglihua Laboratory Animal Technology Co., LTD. Rats were 10-12 weeks old, the weight was 200-250 g and the license number was SCXK (Shanghai) 2017-0011. They were randomly divided into a blank group, combination drug group, trimetazidine group and control group with 10 rats in each group. Rats were given free food intake and drinking water for 12h/ 12h light and dark cycles at 21±2 ℃ for 7 days to adapt to the laboratory environment. The research was approved by the Animal Ethics Committee.

Establishment of DCM rat model

On the 8th day, DCM models were established in the combination drug group, trimetazidine group and control group rats (23). Adriamycin was injected intraperitoneally at a dose of 1 mg/kg twice per week for 6 weeks. Then cardiac function indexes of rats were detected. If left ventricular dysfunction (LVEF≤45%) occurred in rats, the modeling was successful, and the modeling rats did not die. After successful modeling, the rats in the combination drug group were given 4 mg/kg perindopril (Servier Pharmaceutical Co., Ltd., SFDA Approval No. H20034053) and 10 mg/kg trimetazidine (Reyoung Pharmaceutical Co., Ltd., SFDA Approval No. H20066534) by gavage once/d for 4 weeks. Rats in the trimetazidine group were given trimetazidine 10 mg/kg by intragastric administration once/d for 4 weeks. Rats in the control group did not receive any drug intervention.

Examination of rats LEVF, LVEDD and LVESD by echocardiography

Rats in the blank group, combination drug group before modeling and after 4 weeks of drug intervention, trimetazidine group and control group were injected intraperitoneally with 10% chloral hydrate (200 mg/kg) for anesthesia. All the animals did not exhibit signs of peritonitis. The chest area was shaved to remove the body hair, echocardiography was performed (Vivid-iTM ultrasound system, GE, Vivid E9) and LVEDD, LVESD and LVEF values were measured.

Collection and detection of sample

Detection of the expression of BNP and NT-proBNP by ELISA

The kit was obtained from Wuhan Moshake Biotechnology Co., Ltd. with product number KT45631. After echocardiography was obtained for 12 hours, uncondensed blood was taken from orbital venous plexus in rats of blank group, combination drug group, trimetazidine group and control group, anticoagulated with ethylenediaminetetraacetic acid and centrifuged at 13000 r/min for 10min, and then serum was stored at -80 ℃ for testing.

The blank holes, standard holes and sample holes were tested. Standard SO samples with a concentration of 0 were added to the blank wells. The standard sample was added to the standard well. First, add the sample to be tested in the sample well. Sample diluent and and horseradish peroxidase (HRP) were added to all microwells, except for sample wells. Then it rinsed completely to remove border biotinylated antibody. Then added labeled avidin HRP, and re-added the TMB substrate to the coating after washing. TMB turned blue and yellow under the action of catalyst and acid, respectively. The adsorption rate (OD value) was measured with a microplate reader at a wavelength of 450 nm. Then converted the corresponding concentration from standard curve.

Detection of AT1Rs and lamin A expression by RT-PCR

After echocardiography was obtained for 24 hours, the rats were anesthetized with 5% pentobarbital (50 mg/kg; intraperitoneal injection) before sacrifice. Rats in blank group, combination drug group, trimetazidine group and control group were euthanized with 10% potassium chloride (75 mg/kg, intravenous). The heart was removed and washed with phosphate saline, and then the LV free wall was removed. Myocardium was sliced and frozen at -80 ℃. The expression of AT1Rs and lamin A were detected by RT-PCR.

The total RNA was extracted from collected myocardial slices with TRIzol kit (Invitrogen, Carlsbad, California, USA, 15596018). The purity, concentration and integrity of total RNA were detected by UV-Spectrophotometer and agarose gel electrophoresis. Subsequently, reverse transcription was performed according to the instructions by using the TaqMan Reverse reverse transcription kit (Invitrogen, Carlsbad, California, USA, N8080234). The obtained cDNA was further studied. TransStart Green qPCR SuperMix UDG (Beijing TransGen Biotech Co., Ltd., China, AQ111-01) was used for reverse transcription of the extracted total RNA. The steps were carried out according to the kit instructions and cDNA was collected for PCR amplification experiments. The upstream sequence of primer was 5'-GATACTCACTTTTTGCGGTCT-3' and the downstream sequence was 5'-GTGCAGGGTCCGAGGT-3'. The upstream sequence of U6 was 5'-CGCTTCGGCAGCACATATAC-3' and the downstream sequence: 5'-CAGGGGCCATGCTAATCTT -3'. The amplification system of qPCR was as follows: cDNA 1μL, primers at upstream and downstream 0.4μL each, 2×TransStart® Green qPCR SuperMix UDG`10μL, Passive Reference Dye (50X) (optional) 0.4μL, finally adding nuclease-free water for achievement to 20 μL. qPCR amplification conditions were as follows: incubation at 94 °C for 10min, pre-denaturation at 94 °C for 5s, annealing and extension at 60 °C for the 30s, and a total of 40 cycles. 3 repeated wells were set up in every sample. The research was performed 3 times. In this research, GAPDH was applied as an internal parameter. $2^{-\Delta\Delta Ct}$ was used to analyze the data.

Outcome measures

The survival of rats in each group after 4 weeks of drug therapy was observed. The changes of LEVF, LVEDD and LVESD before modeling and after drug treatment were observed. The changes of BNP, NT-

proBNP concentrations and the relative expressions of AT1Rs and lamin A were observed before modeling and after drug therapy.

Statistical analysis

In this study, SPSS20.0 (SPSS Chicago, USA) medical statistical analysis software was used for statistical analysis of the collected data. GraphPad Prism 7 (GraphPad software inc., San Diego, USA) was used to graph the collected data. The measurement data were expressed as mean number ± standard deviation (Meas±SD). All measurement data conformed to normal distribution. One-way ANOVA test was used for comparison among three or more groups, expressed as F. K-M survival was used to analyze the survival of rats within 4 weeks after drug intervention, with the log-rank test. The difference was statistically significant with P< 0.05.

Results

Survival of rats in each group

The survival of rats in each group was observed within 4 weeks after drug treatment. The results showed that no rats died in the blank group, 3 cases died in the control group, 2 cases died in the trimetazidine group and one case died in the combination drug group within 1-2 weeks. In 3-4 weeks, 5 cases died in the control group, 1 case died in the trimetazidine group, and no rats died in the combination drug group. By drawing the K-M survival curve, it was found that the survival of the blank group was significantly higher than that of the control group, trimetazidine group and combination drug group (P< 0.001). The survival of the combination drug group and trimetazidine group was significantly higher than that of the control group (P< 0.001). There was no significant difference between the trimetazidine group and the combination drug group (P> 0.05). More details are shown in Figure 1.

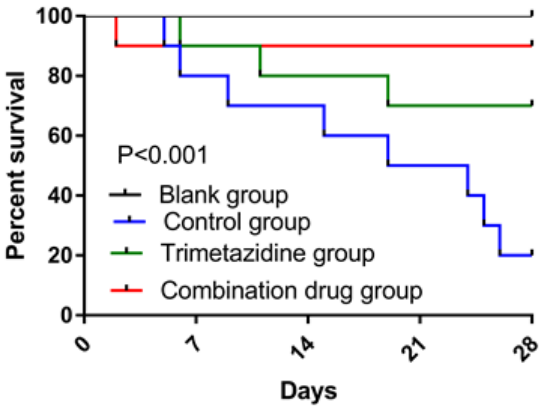

Figure 1. 4-week survival curve of drug treatment. The survival rates of blank group, control group, trimetazidine group and combination drug group were 100, 20, 70, and 90% respectively. The survival of the blank group was significantly higher than that of the control group, trimetazidine group and combination drug group (P< 0.001). The survival of the combination drug group and trimetazidine group was significantly higher than that of the control group (P< 0.001). There was no significant difference between the trimetazidine group and the combination drug group (P> 0.05).

Echocardiographic examination results of rats in each group

By measuring LVEDD, LVESD and LVEF of rats in each group after drug treatment, it was found that LVEDD and LVESD in the combination drug group (5.28±0.81) (2.34±0.29) and trimetazidine group (5.59±0.48) (2.62±0.33) were significantly lower than those in the control group (7.52±0.56) (5.04±0.92) (p < 0.001), and there was no significant difference between them and the blank group (p > 0.05). LVEF values of the combination drug group (55.74±3.23) and trimetazidine group (53.12±2.42) were significantly higher than those of the control group (33.27±2.81) (P< 0.001), and there was no significant difference between them and the blank group (P> 0.05). There was no significant difference in LVEDD, LVESD and LVEF values between the combination drug group and trimetazidine group (P> 0.05). More details are shown in Table 1.

Expressions of BNP and NT-proBNP of rats in each group

By detecting the expressions of BNP and NT-proBNP of rats in each group after 4 weeks of treatment, the expressions of BNP and NT-proBNP in trimetazidine group (329.14±53.68) (1612.17±443.92), combination drug group (274.82±37.53) (1183.71±462.28) and blank group (286.74±16.38) (1218.56±324.73) were significantly lower than those in the control group (457.36±51.24) (2278.34±496.48), and the expressions of BNP and NT-proBNP in the combination drug group were significantly lower than those in trimetazidine group. More details are shown in Figure 2.

Relative expressions of AT1Rs and lamin A of rats in each group

By detecting the relative expressions of AT1Rs and lamin A of rats in each group after 4 weeks of treatment, the relative expressions of AT1Rs in trimetazidine group (1.142±0.131), combination drug group (1.016±0.074) and blank group (1.012±0.092) were significantly lower than those in the control group (1.325±0.178), and the

Table 1. Comparison of LVEDD, LVESD, and LVEF of rats in each group.

Grouping	LVEDD (mm)	LVESD (mm)	LVEF(%)
blank group (n=10)	5.28±0.81	2.34±0.29	55.74±3.23
control group (n=10)	7.52±0.56	5.04±0.92	33.27±2.81
trimetazidine group(n=10)	5.59±0.48	2.62±0.33	53.12±2.42
Combination drug group (n=10)	5.25±0.67	2.30±0.37	56.55±3.17
F	28.520	59.050	142.2
P	<0.001	<0.001	<0.001

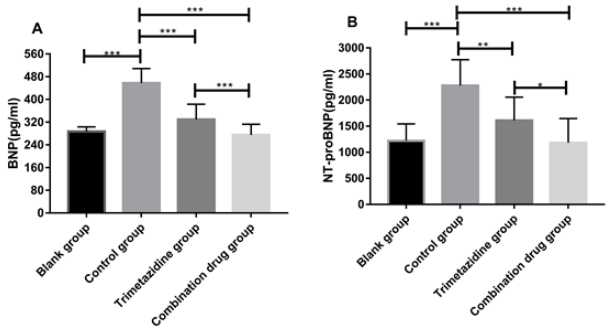

Figure 2. Expressions of BNP and NT-proBNP of rats in each group after 4 weeks of treatment; (**A**): By detecting the expressions of BNP of rats in each group after 4 weeks of treatment, the expressions of BNP in trimetazidine group (329.14±53.68), combination drug group (274.82±37.53) and blank group (286.74±16.38) were significantly lower than those in the control group (457.36±51.24), and the expressions of BNP in combination drug group were significantly lower than those in trimetazidine group, (**B**): The expressions of NT-proBNP in trimetazidine group (1612.17±443.92), combination drug group (1183.71±462.28) and blank group (1218.56±324.73) were significantly lower than those in the control group (2278.34±496.48), and the expressions of NT-proBNP in combination drug group were significantly lower than those in trimetazidine group; * indicates P< 0.05, ** indicates P< 0.01, *** indicates P< 0.001.

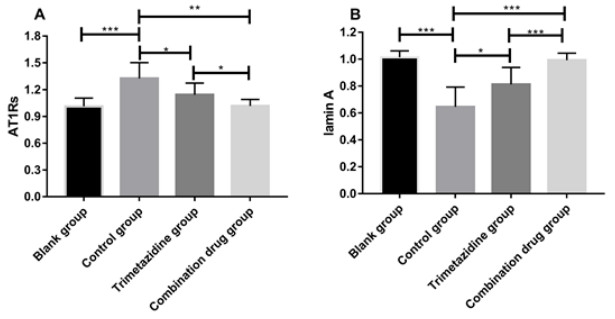

Figure 3. Relative expressions of AT1Rs and lamin A of rats in each group after 4 weeks of treatment; (**A**): By detecting the relative expressions of AT1Rs of rats in each group after 4 weeks of treatment, the relative expressions of AT1Rs in trimetazidine group (1.142±0.131), combination drug group (1.016±0.074) and blank group (1.012±0.092) were significantly lower than those in the control group (1.325±0.178), and the relative expressions of AT1Rs in combination drug group were significantly lower than those in trimetazidine group, (**B**): The relative expressions of lamin A in trimetazidine group (0.812±0.126), combination drug group (0.992±0.052) and blank group (1.014±0.047) were significantly higher than those in the control group (0.645±0.147), and the relative expressions of lamin A in combination drug group were significantly higher than those in trimetazidine group; * indicates P< 0.05, ** indicates P< 0.01, *** indicates P< 0.001.

relative expressions of AT1Rs in the combination drug group were significantly lower than those in trimetazidine group. The relative expressions of lamin A in trimetazidine group (0.812±0.126), combination drug group (0.992±0.052) and blank group (1.014±0.047) were significantly higher than those in the control group (0.645±0.147), and the relative expressions of lamin A in the combination drug group were significantly higher than those in trimetazidine group. More details are shown in Figure 3.

Discussion

DCM has high family heritability and mortality, which brings heavy economic and health burden to patients' families. The diagnosis and treatment of DCM have attracted extensive attention from all sectors of society. Echocardiography is usually used to evaluate left ventricular enlargement and LVEF in the clinical diagnosis of DCM. LVEF<50% is considered as left ventricular systolic dysfunction (24). Studies have shown that perindopril can reduce ATR1s and improve left ventricular remodeling and systolic function (25). Trimetazidine is a metabolic drug that acts on heart disease and has a protective effect on the heart (26). Both are widely used in the treatment of cardiovascular diseases. Studies have confirmed that DCM is related to mutation of lamin A (27). In this study, trimetazidine combined with perindopril will be applied to treat DCM rats to study its effect on the levels of NT-proBNP, AT1Rs and lamin A in rats (27-33).

In this study, we first compared the survival of rats in each group within 4 weeks of drug treatment. The results showed that there was no rat death in the blank group, the survival rate of the combination drug group and trimetazidine group was significantly higher than that of the control group and the survival rate of the combination drug group, blank group and trimetazidine had no difference. This suggested that both perindopril and trimetazidine can treat DCM rats and significantly improve the survival rate. Then we examined the cardiac function of the rats after 4 weeks of treatment by echocardiography. The results showed that LVESD and LVEDD of the combination drug group and trimetazidine group were significantly lower than those of the control group, while LVEF of the combination drug group and trimetazidine group were significantly higher than those of the control group. LVESD, LVEDD and LVEF of the combination drug group and the control group had no significant difference. The research results showed that perindopril and trimetazidine can improve cardiac function and protect the heart in DCM rats. Raj et al. (34) also prove that perindopril can improve cardiac remodeling and reduce systolic dysfunction. The combined application of trimetazidine reduces the metabolic burden on the heart of DCM patients and plays a role in protecting the heart. NT-proBNP, as a biomarker of heart failure, is highly expressed in patients (35), while cardiac cell fibrosis is positively correlated with heart failure (36). We measured the BNP and NT-proBNP levels of DCM rats after 4 weeks of treatment and found that the BNP and NT-proBNP levels in the combination drug group were significantly lower than those in trimetazidine group and control group, and there was no significant difference between them and the blank group, indicating that perindopril combined with trimetazidine is more significant in cardiac function optimization and more obvious clinical effect to treat DCM rats.

In this study, the relative expression level of ART1s was detected in DCM rats after 4 weeks of treatment. It was found that the ART1s level in the combination drug group was significantly lower than that in the control

group and trimetazidine group, and there was no significant difference between them and the blank group. This indicated that the combined treatment had a more obvious effect on lowering the ART1s level, which can significantly increase LVEF and reduce cardiac dysfunction. In the study of Kawai et al. (37), Ang II has an induction effect on the proliferation and migration of mouse cardiac fibroblasts. It can promote cardiac fibrosis. Perindopril, an ACEI, can inhibit the angiotensin-converting enzyme, reduce Ang II and reduce the effect of Ang II-mediated by ATR1s combination, thus reducing left ventricular hypertrophy, improving hemodynamics, increasing LVEF. Combined treatment with trimetazidine can enhance cardiac protection. The etiology of DCM is complex and varied. Mutation of lamin A is a common cause of DCM. At the end of the study, we detected the relative expression level of lamin A after 4 weeks of treatment in DCM rats. It was found that the relative expression of lamin A in the combination drug group and trimetazidine group was significantly higher than that in the control group, and the level of lamin A in combination drug group was significantly higher than that in trimetazidine group, with no significant difference from the blank group. It showed that the combined administration can significantly increase the level of lamin A and reduce the mutation of lamin A. The therapeutic effect was more obvious. This is basically consistent with the study of Narula et al. (38) that confirmed the low expression of lamin A in DCM patients. Maria et al. (39) have also shown that mutations in lamin A can cause myocardial fibrosis and impair left ventricular systolic and diastolic functions. Nikolova et al (29) have also confirmed this point in studies of mice with lamin deficiency.

Although this study was carried out under strict experimental conditions, there are still some deficiencies. First of all, due to the small number of samples included in each group, the experimental results may have errors. Secondly, the inhibition of ACE by perindopril is slower than that by other ACEI, so it may also have a certain effect on the survival rate of rats. Furthermore, the concentration of perindopril used in this study is single. Whether it can improve the prognosis by increasing the drug concentration has not been further studied. Therefore, we hope to increase the number of our samples in future research and study the improvement of the disease by increasing the treatment schemes with different concentrations to supplement our research results.

To sum up, compared with trimetazidine single-agent, trimetazidine combined with perindopril can significantly improve the cardiac function of DCM rats, reduce the serum NT-proBNP level and improve the expression of AT1Rs and lamin A in rats.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
JHL wrote the manuscript. BZ and JLY collected and analyzed general data. LLC helped with statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of The First Affiliated Hospital of Gannan Medical University.

Consent for publication
Not applicable.

Conflict of interest
The authors declare that they have no competing interests.

References

1. Weintraub RG, Semsarian C and Macdonald P: Dilated cardiomyopathy. Lancet 2017; 390: 400-414.
2. Merlo M, Cannatà A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving concepts in dilated cardiomyopathy. Eur J Heart Fail 2018; 20: 228-239.
3. Hershberger RE, Hedges DJ and Morales A. The complexity of a diverse genetic architecture. Nat Rev Cardiol 2013; 10: 531-547.
4. Das S, Biswas A, Kapoor M, Seth S, Bhargava B, Rao VR. Epidemiology of cardiomyopathy–A clinical and genetic study of dilated cardiomyopathy: The EPOCH-D study. J Pract Cardiovasc Sci 2015; 1;1:30.
5. Lakdawala NK, Winterfield JR, Funke BH. Dilated cardiomyopathy. Circ Arrhythm Electrophysiol 2013; 6: 228-237.
6. Liang Y, Lin Q, Huang P, Wang Y, Li J, Zhang L, Cao J. Rice Bioactive Peptide Binding with TLR4 To Overcome H2O2-Induced Injury in Human Umbilical Vein Endothelial Cells through NF-κB Signaling. J Agri Food Chem 2018; 66(2): 440-448.
7. Wang L, Lin Q, Yang T, Liang Y, Nie Y, Luo Y, Luo F. Oryzanol modifies high fat diet-induced obesity, liver gene expression profile, and inflammation response in mice. J Agri Food Chem 2017; 65(38): 8374-8385.
8. Lou Y, Shi J, Guo D, Qureshi AK, Song L. Function of PD-L1 in antitumor immunity of glioma cells. Saudi J Biol Sci 2017; 24(4): 803-807.
9. Guo T, Lin Q, Li X, Nie Y, Wang L, Shi L, Luo F. Octacosanol attenuates inflammation in both RAW264. 7 macrophages and a mouse model of colitis. J Agri Food Chem 2017; 65(18): 3647-3658.
10. Li W, Jia MX, Wang JH, Lu JL, Deng J, Tang JX, Liu C. Association of MMP9-1562C/T and MMP13-77A/G polymorphisms with non-small cell lung cancer in southern Chinese population. Biomol 2019; 9(3): 107-119.
11. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest 2013; 123: 19-26.
12. Bera M, Kumar R, Sinha B, Sengupta K. Nuclear deformation and anchorage defect induced by DCM mutants in lamin A. bioRxiv 2019; 1:611665.
13. Van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, Van Der Kooi AJ, Van Tintelen JP, Van Den Berg MP, Pilotto A, Pasotti M, Jenkins S. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: a European cohort study. J Am Coll Cardiol 2012; 31;59(5):493-500.
14. Mathew T, Williams L, Navaratnam G, Rana B, Wheeler R, Collins K, Harkness A, Jones R, Knight D, O'Gallagher K, Oxborough

D. Diagnosis and assessment of dilated cardiomyopathy: a guideline protocol from the British Society of Echocardiography. Echo Res Pract 2017; 4: G1-G13.
15. Madamanchi C, Alhosaini H, Sumida A and Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. Int J Cardiol 2014; 176: 611-617.
16. Koura HM, Abdalla NM, Hamed Ibrahim M, Abo Hashish MM and Zaki SM. NT-proBNP in children with left to right shunt and dilated cardiomyopathy. Iran J Pediatr 2016; 26: e4485.
17. von Lueder TG, Sangaralingham SJ, Wang BH, Kompa AR, Atar D, Burnett JC Jr, Krum H. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. Circ Heart Fail 2013; 6: 594-605.
18. Vardeny O, Tacheny T, Solomon SD. First-in-class angiotensin receptor neprilysin inhibitor in heart failure. Clin Pharmacol Ther 2013; 94: 445-448.
19. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR. Paradigm-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). Eur J Heart Fail 2013; 15: 1062-1073.
20. Kubo T, Matsumura Y, Kitaoka H, Okawa M, Hirota T, Hamada T, Hitomi N, Hoshikawa E, Hayato K, Shimizu Y, Yamasaki N. Improvement in prognosis of dilated cardiomyopathy in the elderly over the past 20years. J Cardiol 2008; 52: 111-117.
21. Du Q, Wu J, Wang H, Wang X, Xu L, Zhang Z, Liu J, Zhang J, Chen J, Hakonarson H, Hu A, Zhang L. Perindopril treatment promote left ventricle remodeling in patients with heart failure screened positive for autoantibodies against angiotensin II type 1 receptor. BMC Cardiovasc Disord 2013; 13: 94-101.
22. Zhang L, Ding WY, Wang ZH, Tang MX, Wang F, Li Y, Zhong M, Zhang Y, Zhang W. Early administration of trimetazidine attenuates diabetic cardiomyopathy in rats by alleviating fibrosis, reducing apoptosis and enhancing autophagy. J Transl Med 2016; 14: 109.
23. Shen LJ, Lu S, Zhou YH, Li L, Xing QM, Xu YL. Developing a rat model of dilated cardiomyopathy with improved survival. J Zhejiang Univ Sci 2016; B 17: 975-983.
24. Hershberger RE, Morales A. Dilated cardiomyopathy overview. Genereviews[internet]. University of Washington, Seattle, 2018.
25. Hao P, Yang J, Liu Y, Zhang M, Zhang K, Gao F, Chen Y, Zhang C, Zhang Y. Combination of angiotensin-(1–7) with perindopril is better than single therapy in ameliorating diabetic cardiomyopathy. Sci Rep 2015; 5: 8794.
26. Tsioufis K, Andrikopoulos G, Manolis A. Trimetazidine and cardioprotection: facts and perspectives. Angiology 2015; 66: 204-210.
27. Cattin ME, Ferry A, Vignaud A, Mougenot N, Jacquet A, Wahbi K, Bertrand AT, Bonne G. Mutation in lamin A/C sensitizes the myocardium to exercise-induced mechanical stress but has no effect on skeletal muscles in mouse. Neuromuscul Disord 2016; 26: 490-499.
28. Nie Y, Luo F, Wang L, Yang T, Shi L, Li X, Shen J, Xu W, Guo T, Lin Q. Anti-hyperlipidemic effect of rice bran polysaccharide and its potential mechanism in high-fat diet mice. Food Func 2017; 8(11): 4028-4041.
29. Lou Y, Yang J, Wang L, Chen X, Xin X, Liu Y. The clinical efficacy study of treatment to Chiari malformation type I with syringomyelia under the minimally invasive surgery of resection of Submeningeal cerebellar Tonsillar Herniation and reconstruction of Cisterna magna. Saudi J Biol Sci 2019; 26(8): 1927-1931.
30. Lou Y, Guo D, Zhang H, Song L. Effectiveness of mesenchymal stems cells cultured by hanging drop vs. conventional culturing on the repair of hypoxic-ischemic-damaged mouse brains, measured by stemness gene expression. Open Life Sci 2016; 11(1): 519-523.
31. Chen X, Xu Y, Meng L, Chen X, Yuan L, Cai Q, Shi W, Huang G. Non-parametric partial least squares–discriminant analysis model based on sum of ranking difference algorithm for tea grade identification using electronic tongue data identify tea grade using e-tongue data. Sens Actuators B Chem 2020; 127924.
32. Nie Y, Luo F, Lin Q. Dietary nutrition and gut microflora: A promising target for treating diseases. Trends Food Sci Technol 2018;75: 72-80.
33. Ren Y, Jiao X, Zhang L. Expression level of fibroblast growth factor 5 (FGF5) in the peripheral blood of primary hypertension and its clinical significance. Saudi J Biol Sci 2018; 25(3): 469-473.
34. Raj P, Aloud BM, Louis XL, Yu L, Zieroth S, Netticadan T. Resveratrol is equipotent to perindopril in attenuating post-infarct cardiac remodeling and contractile dysfunction in rats. J Nutr Biochem 2016; 28: 155-163.
35. McKie PM, Burnett JC. NT-proBNP: the gold standard biomarker in heart failure. J Am Coll Cardiol 2016; 68: 2437-2439.
36. Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JP, Schroen B, André S, Crijns HJ, Gabius HJ, Maessen J, Pinto YM. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation 2004; 110: 3121-3128.
37. Kawai T, Forrester SJ, O'Brien S, Baggett A, Rizzo V, Eguchi S. AT1 receptor signaling pathways in the cardiovascular system. Pharmacol Res 2017; 125: 4-13.
38. Narula N, Favalli V, Tarantino P, Grasso M, Pilotto A, Bellazzi R, Serio A, Gambarin FI, Charron P, Meder B, Pinto Y. Quantitative expression of the mutated lamin A/C gene in patients with cardiolaminopathy. J Am Coll Cardiol 2012; 60: 1916-1920.
39. Chatzifrangkeskou M, Le Dour C, Wu W, Morrow JP, Joseph LC, Beuvin M, Sera F, Homma S, Vignier N, Mougenot N, Bonne G. ERK1/2 directly acts on CTGF/CCN2 expression to mediate myocardial fibrosis in cardiomyopathy caused by mutations in the lamin A/C gene. Hum Mol Genet 2016; 25: 2220-2233.
40. Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalicek J, Otway R, Verheyen F, Rainer S. Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C–deficient mice. J Clin Invest 2004; 113: 357-369.