European Review for Medical and Pharmacological Sciences 2019; 23: 8095-8100

The relevance of *HIF1A* gene polymorphisms and primary hypertensive left ventricular hypertrophy in Chinese Han population

Z.-L. SHENG, C.-W. JU, G.-L. YAN, Z.-P. CHEN, X.-D. PAN, W.-B. LU, Y.-Y. YAO, G.-S. MA

Department of Cardiology, Zhongda Hospital, Medical School of Southeast University, Nanjing, China

Zulong Sheng and Chenwei Ju contributed equally to this work

Abstract. – INTRODUCTION: To investigate the effect of gene polymorphisms in *hypoxia-inducible factor 1*α (*HIF-1*α) in left ventricular hypertrophy of hypertensive patients.

PATIENTS AND METHODS: A total of 583 hypertensive patients were divided into two groups, with left ventricular hypertrophy (LVH (+), 198 cases) and without left ventricular hypertrophy (LVH (-), 385 cases). Polymerase Chain Reaction restriction fragment length polymorphism was used to detect the single nucleotide gene polymorphisms rs11549465, rs11549467 and rs1957757 in *HIF-1*α.

RESULTS: The distribution differences of gene frequencies for rs11549465, rs11549467 and rs1957757 in HIF1A single nucleotide gene polymorphisms for LVH (+) and LVH (-) were statistically significant ($p<0.05$). The T allele of rs11549465 loci and the G allele of rs11549467 loci increased the risk of LVH, related to the increased plasma expression of *HIF-1*α ($p<0.05$).

CONCLUSIONS: Gene polymorphism of *HIF-1*α were related to primary hypertensive left ventricular hypertrophy, and the expression of rs11549467 correlated with the increasing concentration of plasma *HIF-1*α.

Key Words:
Hypertension left ventricular hypertrophy, *HIF-1*α, Single nucleotide polymorphism.

Introduction

Left ventricular hypertrophy (LVH) is a common form of organ damage in hypertension, and it is an independent risk predictor for mortality and morbidity of cardiovascular disease[1]. Hammond et al[2] showed that the incidence of LVH in patients with borderline hypertension was approximately 12% and was 20% in patients with mild hypertension. Epidemiological data in China showed that the incidence of LVH in patients with primary hypertension was approximately 25%-35%[3]. LVH leads to blood stasis in the heart, arrhythmias such as atrial fibrillation, cardiac failure, thrombus formation and increased risk of ischaemic stroke[4]. Furthermore, for every 50 g increase in LVH, the mortality of cardiovascular disease increased 1.73-fold in men and 2.12-fold in women[5].

The evidence shows that LVH is a long-term response in the heart to various stimuli, including increased hemodynamic loads, neurohormonal activation, metabolic related factors (ischemia and hypoxia), and local hormone and cytokine release by myocardial tissue. Hypoxia-inducible factor 1 (HIF-1) is a heterodimeric transcription factor composed of HIF-1α and HIF-1β. HIF-1α is widely expressed in the heart tissue, not only the regulatory subunit of HIF-1 but also the active subunit. Therefore, the biological effects of HIF-1 are attributable to the α subunit, participating in the regulation of myocardial hypertrophy under hypoxia or stimulation[6]. Furthermore, a large number of researches[7] have shown that many candidate genes were involved in the generation and development of LVH in various ethnic groups. Among them, the stable expression of *HIF1-α* gene plays an important role in maintaining the response of myocardial tissue cells to hypoxia. Therefore, the correlation between *HIF1-α* gene polymorphisms and primary hypertension LVH was investigated in this work.

Patients and Methods

Inclusion of Research Objects

A total of 583 patients with primary hypertension were enrolled from January 2013 to January 2018 in our hospital. Depending on whether they had complicated LVH, the patients were divided into the primary hypertension group (LVH (-)) and the primary hypertension LVH group (LVH (+)). This

Corresponding Author: Zulong Sheng, MM; e-mail: shengzulong@126.com

investigation was approved by the Ethics Committee of Zhongda Hospital, Medical School of Southeast University. The signed written informed consents were obtained from all participants before the study.

The Diagnostic Criteria of LVH (+)

The left ventricular mass index (LVMI) was calculated by the echocardiographic results and the Devereux formula. LVMI ≥125 g/m^2 for men and LVMI ≥110 g/m^2 for women were criteria for LVH (+).

Exclusion Criteria

First, patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, immune diseases involving the heart and other related myocardial diseases were excluded. Second, patients with diseases that caused secondary myocardial hypertrophy, including valvular heart disease, pulmonary artery hypertension, ischemic cardiomyopathy, and congenital heart disease were excluded. Third, patients with secondary hypertension diseases, including renoparenchymal hypertension, renal artery stenosis, primary aldosteronism, pheochromocytoma, Cushing's syndrome, and hyperthyroidism were excluded. Fourth, patients with chronic wasting disease, including diseases associated with a malignant tumor were excluded as were patients with multiple organ failure. Fifth, patients with diseases associated with liver, kidney diseases, and abnormal liver and kidney functions were excluded.

Experimental Methods

General data collection

We collected and recorded age, gender, smoking status, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

DNA extraction from peripheral blood leukocytes (PWBC)

Fasting 5 ml peripheral antecubital venous samples were collected from the acute myocardial infarction (AMI) group and the normal control group. The blood samples were placed in the ethylenediaminetetraacetic acid (EDTA) anticoagulation tubes and were stored at -20°C. The DNA of PWBC was extracted by the phenol-chloroform organic extraction method, dissolved in TE buffer, and stored at -4°C.

The detection methods

HIF1A SNPs were selected on the basis of the public HapMap SNP database (http://www.hapmap.org) and the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), with the criteria of minor allele frequency (MAF) >5% in the Chinese Han population. Three SNPs (rs11549465, rs11549467, rs1957757) were chosen for genotyping. The Polymerase Chain Reaction restriction fragment length polymorphism (PCR-RFLP) was used in the genotyping of three alleles (rs11549465, rs11549467, rs1957757) in *HIF1A*. The details, according to the following instructions, were: a 10 μL PCR reaction was prepared for each sample, 1 μL 10× PCR buffer including 15 mM $Mg2^+$ (TaKaRa, Otsu, Shiga, Japan), 1 μL 0.2 mM dNTPs mixture, 1 U HotStarTaq polymerase (Qiagen, Hilden, Germany), 1 μL sample DNA (10 μM), 1 μL forward primer (10 μM), 1 μL reverse primer (10 μM) and added RNase free dH2O up to 10 μL. PCR reaction conditions were divided into several steps: 95°C for 2 min; 11 cycles of 94°C for 20 s, 65°C for 40 s, 72°C for 1.5 min; 24 cycles of 94°C for 20 s, 59°C for 30 s, 72°C for 1.5 min, and a final extension at 72°C for 2 min and stored at 4 °C for the next step. A volume of 10 μL PCR products were purified with 5 U of shrimp alkaline phosphatase and 2 U of exonuclease I (Qiagen, Hilden, Germany), 37°C for an hour and inactivation at 75°C for 15 min. Two allele-specific fluorescently labeled probes were used for the SNP detection within 1 μL of 10 × binding buffer, 2 μL of multiplex PCR product, 0.25 μL of thermostable Taq DNA ligase (TaKaRa, Otsu, Shiga, Japan), 0.4 μL of 5′ ligation primer (1 μM), 0.4 μL of 3′ ligation primer (2 μM), 6 μL of RNase free dH2O and the reaction needs a 38 cycles of 94 °C for 1 min, 58 °C for 4 min and maintained at 4°C. Data were analyzed with GeneMapper Software v.4.1 (Applied Biosystems, Foster City, CA, USA). All genotyping was performed with a double blinding method and there was 100% consistency for the 10% randomly repeated experiments. The tumor necrosis factor (TNF)-related weak inducer of apoptosis (TWEAK) was measured by enzyme-linked immunosorbent assay (ELISA). Total cholesterol (TC), triglyceride, (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (Glu) were measured by the Olympus automatic biochemistry analyzer.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 13.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The measurement data were expressed as mean ± standard deviation. The enumeration data were expressed as rate (%), and

Table I. Comparison of baseline levels between two groups.

Variable	LVH (+)	LVH (-)	*p*-value
Age (year)	63.61±12.7	64.6±11.5	NS
Men (n, %)	121(61.1%)	246(63.9%)	NS
Smokers (n, %)	145 (73.2%)	281 (73.0%)	NS
BMI (kg/m^2)	26.6±9.4	25.8±10.1	NS
SBP (mmHg)	150.3±7.8	148.3±9.6	NS
DBP (mmHg)	86.7±5.6	84.9±7.1	NS
TG (ng/dl)	5.8 ±1.3	5.7 ±1.6	NS
HDL-C (ng/dl)	1.5±0.5	1.6±0.6	NS
LDL-C (ng/dl)	2.5±0.2	2.4±0.3	NS
sHIF1-alpha (pg/ml)	32.7±12.5	39.9±11.4	<0.05

the pairwise comparison of *t*-tests was adopted for the comparison of cardinality level. Allelic frequencies of each polymorphic loci were tested by Hardy-Weinberg equilibrium and compared by the chi-square test. The genotype distribution, allele frequency, and genotype distribution frequency of LVH (-) and LVH (+) were expressed by the odds ratio (OR) and 95% confidence interval (95% CI). Differences were statistically significant at $p<0.05$.

Results

Comparison of Baseline Levels Between Two Groups

The baseline levels between the two groups are shown in Table I. A total of 385 patients were included in the LVH (-) group, with 246 men and 139 women, average age 64.6±11.5 years old; there were 281 smokers. A total of 198 patients were included in the LVH (+) group, with 121 men and 77 women, average age 63.61±12.7 years old; 145 were smokers. There were no significant differences in terms of age, gender, BMI, SBP, DBP, TG, HDL-C, or LDL-C between the groups ($p>0.05$). However, there was a significant difference in plasma HIF1-α levels between the two groups ($p<0.05$).

The Genotype Distribution of SNPs in HIF1A

All patients were measured in this study, and all genotype distribution frequencies followed Hardy-Weinberg equilibrium. The sequencing results showed (Table II) that the three genotype frequencies (TT, CT, CC) of alleles rs11549465 in *HIF1A* in the LVH (+) group were 7.6%, 49.5% and 42.9%, respectively and 4.9%, 41.3% and 53.8% in the LVH (-) group, respectively. There were significant differences in genotype frequency distribution between the two groups ($p<0.05$). The three genotype frequencies (GG, GA, AA) of alleles rs11549467 in *HIF1A* in the LVH (+) group were 13.6%, 49.0% and 37.4%, respectively, and 7.8%, 47.3% and 44.9% in the LVH (-) group. There were significant differences in genotype frequency distributions between the two groups ($p<0.05$). However, there were no significant differences in genotype frequency distributions of rs1957757 between the two groups ($p>0.05$).

Table II. The genotype distribution of SNPs in *HIF1A*.

SNPs	Genotype	LVH (+)	LVH (-)	*p*
rs11549465	TT	15 (7.6%)	19 (4.9%)	0.04
	CT	98 (49.5%)	159 (41.3%)	
	CC	85 (42.9%)	207 (53.8%)	
rs11549467	GG	27 (13.6%)	30 (7.8%)	0.04
	GA	97 (49.0%)	182 (47.3%)	
	AA	74 (37.4%)	173 (44.9%)	
rs1957757	TT	45 (22.7%)	63 (16.4%)	0.06
	TC	92 (46.5%)	171 (45.1%)	
	CC	61 (30.8%)	151 (36.4%)	

Table III. The allele frequency distribution of SNPs in HIFA between two groups.

SNPs	Allele	LVH (+)	LVH (-)	OR (95%CI)	p
rs11549465	T	128 (32.3%)	197 (25.6%)	1.26 (1.05-1.53)	0.02
	C	268 (67.7%)	573 (74.4%)	0.90 (0.84-0.98)	
rs11549467	G	151 (38.1%)	242 (31.4%)	1.21 (1.03-1.43)	0.03
	A	245 (61.9%)	528 (68.6%)	0.90 (0.82-0.99)	
rs1957757	T	183 (46.0%)	297 (38.6%)	1.20 (1.04-1.37)	0.02
	C	215 (54.0%)	473 (61.4%)	0.88 (0.79-0.98)	

There was a difference in allelic frequencies of the three *HIF1A* loci between the two groups. The T and C allelic frequencies in rs11549465 of *HIF1A* in the LVH (+) group were 32.3% and 67.7%, respectively, and they were 25.6% and 74.4% in the LVH (-) group, respectively. T alleles and loci increased the risk of LVH (OR=1.26, 95% CI = (1.05-1.53)), and the difference between the two groups was statistically significant (p<0.05). The G and A allelic frequencies in rs11549467 of *HIF1A* in the LVH (+) group were 38.1% and 61.9%, respectively, and were 31.4% and 68.6% in the LVH (-) group, respectively. G alleles and loci increased the risk of LVH (OR=1.21, 95% CI=(1.03-1.43)), and the difference between the groups was statistically significant (p<0.05). The T and A allelic frequencies in rs1957757 of *HIF1A* in the LVH (+) group were 46.0% and 54.0%, respectively, and were 38.6% and 61.4% in the LVH (-) group, respectively. The difference between the two groups was statistically significant (p<0.05). All results are shown in Table III.

Correlation Analyses Between the Plasma HIF1-α Level and the Dominant Gene Model Genotype Distribution

In the dominant gene model, there was significant difference in rs11549467 and rs1957757 genotype distribution between the groups (p<0.05) (Table IV). The GG genotype of rs11549467 loci gave a higher risk of LVH (OR = 1.75, 95% CI = (1.07-2.86)). Furthermore, the plasma HIF1-α concentrations of GG genotype patients with rs11549467 loci in the LVH (+) group were higher than those of the GA+AA genotype patients and LVH (-) patients (p<0.05).

Discussion

Correlation Between the Primary Hypertension LVH and the HIF1A Gene Polymorphism

Hypertension is the most common cause of LVH, but not all hypertensive patients develop LVH, suggesting that LVH does not depend solely on the onset and severity of hypertension[8]. *HIF1A* is involved in the occurrence and development of many cardiovascular diseases. In this work, LVH was found to be associated with the *HIF1A* gene polymorphism in primary hypertension, especially the GG genotype of rs11549467 and TT genotype of rs1957757 in the dominant gene model. Studies have shown that cardiovascular disease[9] is closely associated with *HIF1A* gene polymorphisms, including ischemic heart disease, coronary artery disease (CAD), stable angina, and acute myocardial infarction[10]. Among these polymorphisms, the rs1957757and rs11549465 loci increased the risk of coronary artery disease development[11,12], and the gene polymorphisms of rs11549465 loci were related to ischemic heart disease[13].

Table IV. The distribution of dominant gene model in the SNPs of HIFA.

SNPs	Genotype	LVH (+)	LVH (-)	OR (95%CI)	p-value
rs11549465	TT	15 (7.6%)	19 (4.9%)	1.54 (0.80-2.96)	0.20
	CT+CC	183 (92.4%)	366 (95.1%)	0.97 (0.93-1.02)	
rs11549467	GG	27 (13.6%)	30 (7.8%)	1.75 (1.07-2.86)	0.02
	GA+AA	171 (86.4%)	355 (92.2%)	0.94 (0.88-0.99)	
rs1957757	TT	45 (22.7%)	63 (16.4%)	1.4 (0.99-1.96)	0.07
	TC+CC	153 (77.3%)	322 (83.6%)	0.93 (0.85-1.0)	

Table V. The correlation analysis of plasma HIF1-α level and the dominant gene model genotype distribution of rs11549467 loci.

Loci	LVH (+)	LVH (-)
rs11549467		
GG	39.7±10.3#*	33.7±10.8
GC+CC	33.8±15.03	32.1±14.13
rs1957757		
TT	33.2±10.9	32.1±12.1
TC+CC	32.9±11.3	32.3±11.3

#Compared to the LVH (-) group, $p<0.05$; *Compared to GG+CC, $p<0.05$

Mechanism of HIF1-α Promoting Myocardial Hypertrophy

Hypoxia is one of the principal pathological mechanisms of myocardial hypertrophy. It is caused by the imbalance between the growth rate of blood vessels and increased heart volume, causing the blood and oxygen supply to the myocardial tissue to become relatively insufficient. HIF1-α is involved in the regulation of myocardial hypertrophy by hypoxia-induced mitogenic factor (HIMF), a transcriptional regulator. LVH is an adaptation to hypertension and is an independent risk predictor for clinical cardiac failure, sudden cardiac death and myocardial infarction[14,15], usually characterized by an increase in the thickness of the left ventricular wall.

HIF1-α was involved in cardiac energy metabolism and glycolipid conversion in pathological myocardial hypertrophy[16]. Hypertensive LVH is often accompanied by abnormalities in myocardial glucose and lipid metabolism, as well as an increased expression of HIF1-α[17]. A study showed that the expression of HIF1-α in hypertrophic cardiomyopathy (HCM) patients and HCM mice was elevated. HIF1-α increases glycolytic flux and glycolipid conversion, promotes cardiomyocyte apoptosis and causes contraction dysfunction by activating glycolytic-related genes, peroxisome proliferator-activated receptor (PPAR), and the glycerol 3 phosphate dehydrogenase pathway. HIF1-α knockout mice are resistant to myocardial hypertrophy and cardiac dysfunction caused by transaortic constriction (TAC)[18]. Increased HIF1-α expression stimulates the conversion of fat to glucose in myocardial tissue. Although this conversion reduces the oxygen consumption to some extent, the accumulation and toxicity of fatty acid further exacerbate the cardiac hypertrophy[15]. Some researches have shown that the apigenin[17] and chrysanthemum extract improves rat myocardial hypertrophy by inhibiting the expression of HIF1-α in myocardial tissue.

HIF1-α also mediates the expression of Cu-dependent VEGF in cardiomyocytes, thus participating in the regulation of myocardial hypertrophy[19]. Mild hypoxia promotes the upregulation of HIF1-α-mediated transient receptor potential canonical channels (TRPC) type 3 and 6 and then promotes the activation of the downstream calcineurin signaling pathway to participate in hypoxic-induced myocardial hypertrophy[20].

Studies have shown that HIF1-α has a protective effect on pathological cardiac dysfunction. HIF1-α and PPARγ participated in the regulation of myocardial metabolism in pregnant rats with cardiac hypertrophy[16]. Specific knockout of HIF1-α in myocardial fibers reduced myocardial contractile function, decreased angiogenesis and abnormal expression of related genes[21]. HIF1-α knockout also affected regulation of the heart function in offspring. After the *HIF1-α* gene was knocked out, the offspring of pregnant diabetic rats showed left ventricular cardiac dysfunction at the 12th week, characterized by myocardial structural remodeling and shortening of myocardial length, as well as increased infiltration of myocardial macrophages and cardiomyocyte apoptosis[22]. Therefore, the mechanism of the effect of HIF1-α on adaptive myocardial hypertrophy needs to be further explored.

Conclusions

There was a correlation between the *HIF1A* gene polymorphisms and the occurrence of the primary hypertension LVH. The rs11549467 locus was correlated with the increase in plasma HIF1-α.

Funding Acknowledgements

This work was supported by the National Nature Science Foundation of the People's Republic of China (No. 81400225 for Zulong Sheng) and the Jiangsu Provincial Medical Youth Talent (QNRC2016815).

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Ramaswamy PK, Bhanukumar M, Hathur B, Shashidhara KC, Srinath KM. Factors contributing to development and reversal of LVH: a pilot study. J Clin Diagn Res 2016; 10: C17-C20.

2) Hammond IW, Devereux RB, Alderman MH, Lutas EM, Spitzer MC, Crowley JS, Laragh JH. The prevalence and correlates of echocardiographic left ventricular hypertrophy among employed patients with uncomplicated hypertension. J Am Coll Cardiol 1986; 7: 639-650.
3) Xu X, Hou X, Liang Y, Li F, Pang L, Huang G, Huang J, Shi M, Sun X, Wang Y. The gene polymorphism of LOX1 predicts the incidence of LVH in patients with essential hypertension. Cell Physiol Biochem 2014; 33: 88-96.
4) Erkuner O, Dudink EAMP, Nieuwlaat R, Rienstra M, Van Gelder IC, Camm AJ, Capucci A, Breithardt G, LeHeuzey JY, Lip GYH, Crijns HJGM, Luermans JGLM. Effect of systemic hypertension with versus without left ventricular hypertrophy on the progression of atrial fibrillation (from the Euro Heart Survey). Am J Cardiol 2018; 122: 578-583.
5) Woroniecki RP, Kahnauth A, Panesar LE, Supe-Markovina K. Left ventricular hypertrophy in pediatric hypertension: a mini review. Front Pediatr 2017; 5: 101.
6) Gao T, Zhu ZY, Zhou X, Xie ML. Chrysanthemum morifolium extract improves hypertension-induced cardiac hypertrophy in rats by reduction of blood pressure and inhibition of myocardial hypoxia inducible factor-1alpha expression. Pharm Biol 2016; 54: 2895-2900.
7) Hou X, Hu Z, Huang X, Chen Y, He X, Xu H, Wang N. Serum osteopontin, but not OPN gene polymorphism, is associated with LVH in essential hypertensive patients. J Mol Med (Berl) 2014; 92: 487-495.
8) Katholi RE, Couri DM. Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications. Int J Hypertens 2011; 2011: 495349.
9) Zheng ZL, Hwang YH, Kim SK, Kim S, Son MJ, Ro H, Sung SA, Lee HH, Chung WK, Joo KW, Yang J. Genetic polymorphisms of hypoxia-inducible factor-1 alpha and cardiovascular disease in hemodialysis patients. Nephron Clin Pract 2009; 113: c104-c111.
10) Gladek I, Ferdin J, Horvat S, Calin GA, Kunej T. HIF1A gene polymorphisms and human diseases: graphical review of 97 association studies. Genes Chromosomes Cancer 2017; 56: 439-452.
11) Sarzynski MA, Rankinen T, Sternfeld B, Grove ML, Fornage M, Jacobs DR, Sidney S, Bouchard C. Association of single-nucleotide polymorphisms from 17 candidate genes with baseline symptom-limited exercise test duration and decrease in duration over 20 years: the Coronary Artery Risk Development in Young Adults (CARDIA) fitness study. Circ Cardiovasc Genet 2010; 3: 531-538.
12) Liu Q, Liang Y, Zou P, Ni WX, Li YG, Chen SM. Hypoxia-inducible factor-1alpha polymorphisms link to coronary artery collateral development and clinical presentation of coronary artery disease. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2013; 157: 340-345.
13) Resar JR, Roguin A, Voner J, Nasir K, Hennebry TA, Miller JM, Ingersoll R, Kasch LM, Semenza GL. Hypoxia-inducible factor 1alpha polymorphism and coronary collaterals in patients with ischemic heart disease. Chest 2005; 128: 787-791.
14) Kumar S, Wang G, Liu W, Ding W, Dong M, Zheng N, Ye H, Liu J. Hypoxia-induced mitogenic factor promotes cardiac hypertrophy via calcium-dependent and hypoxia-inducible factor-1alpha mechanisms. Hypertension 2018; 72: 331-342.
15) Moroni C, Tolone S, Lopreiato F, Scrofani AR, Bossini A, Affricano C, Cassone R, Gaudio C. Effects of losartan on left ventricular mass: a three-year follow-up in elderly hypertensives with myocardial hypertrophy despite successful conventional antihypertensive treatment. Eur Rev Med Pharmacol Sci 2017; 21: 1323-1328.
16) Mirtschink P, Krek W. Hypoxia-driven glycolytic and fructolytic metabolic programs: pivotal to hypertrophic heart disease. Biochim Biophys Acta 2016; 1863: 1822-1828.
17) Zhu ZY, Gao T, Huang Y, Xue J, Xie ML. Apigenin ameliorates hypertension-induced cardiac hypertrophy and down-regulates cardiac hypoxia inducible factor-lalpha in rats. Food Funct 2016; 7: 1992-1998.
18) Krishnan J, Suter M, Windak R, Krebs T, Felley A, Montessuit C, Tokarska-Schlattner M, Aasum E, Bogdanova A, Perriard E, Perriard JC, Larsen T, Pedrazzini T, Krek W. Activation of a HIF1alpha-PPARgamma axis underlies the integration of glycolytic and lipid anabolic pathways in pathologic cardiac hypertrophy. Cell Metab 2009; 9: 512-524.
19) Jiang Y, Reynolds C, Xiao C, Feng W, Zhou Z, Rodriguez W, Tyagi SC, Eaton JW, Saari JT, Kang YJ. Dietary copper supplementation reverses hypertrophic cardiomyopathy induced by chronic pressure overload in mice. J Exp Med 2007; 204: 657-666.
20) Chu W, Wan L, Zhao D, Qu X, Cai F, Huo R, Wang N, Zhu J, Zhang C, Zheng F, Cai R, Dong D, Lu Y, Yang B. Mild hypoxia-induced cardiomyocyte hypertrophy via up-regulation of HIF-1alpha-mediated TRPC signalling. J Cell Mol Med 2012; 16: 2022-2034.
21) Huang Y, Hickey RP, Yeh JL, Liu D, Dadak A, Young LH, Johnson RS, Giordano FJ. Cardiac myocyte-specific HIF-1alpha deletion alters vascularization, energy availability, calcium flux, and contractility in the normoxic heart. FASEB J 2004; 18: 1138-1140.
22) Cerychova R, Bohuslavova R, Papousek F, Sedmera D, Abaffy P, Benes V, Kolar F, Pavlinkova G. Adverse effects of Hif1a mutation and maternal diabetes on the offspring heart. Cardiovasc Diabetol 2018; 17: 68.