

# Transient receptor potential canonical 5 channel is involved in the cardiac damage related to obstructive sleep apnea-hypopnea syndrome in rats

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**Background:** Obstructive sleep apnea-hypopnea syndrome (OSAHS) is recognized as an independent risk factor of cardiovascular disease. The release of  $Ca^{2+}$  mediated by transient receptor potential canonical (TRPC) channels participates in the hypoxia-induced pathophysiological changes in the cardiovascular systems in case of OSAHS. This study aimed to investigate which subtypes of TRPCs were involved in OSAHS in a rat model of intermittent hypoxia.

**Methods:** OSAHS was induced by exposure of rats to intermittent hypoxia. The expression of TRPC-related genes and proteins in the cardiomyocytes by qRT-PCR and Western Blotting, respectively.

**Results:** The mRNA expression of TRPC3/TRPC4/TRPC5 increased significantly in OSAHS group compared with the control group (P<0.05). The TRPC5 protein expression was significantly higher in the OSAHS control than the control group (P<0.05).

**Conclusions:** The TRPC5 channel is likely to be involved in the OSAHS induced pathophysiological changes in the myocardium and may become a target to prevent OSAHS related cardiac damage.

**Keywords:** Obstructive sleep apnea-hypopnea syndrome (OSAHS); intermittent hypoxia; transient receptor potential canonical; calcium; cardiomyocytes

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# Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) as an independent risk factor for cardiovascular diseases is closely related to the development of many cardiovascular diseases such as left ventricular remodeling (1), vascular endothelial injury (2), coronary heart disease, congestive heart failure (3), and arrhythmia (4,5). It is well known that the intermittent hypoxia is involved in the pathogenesis of

OSAHS. Hypoxia may activate the sympathetic nerves and the renin angiotensin-aldosterone system (RAAS), leading to the vasoconstriction and subsequent hypertension. In addition, the fluctuation of intrathoracic negative pressure due to obstruction of the upper airway causes the mechanical and hemodynamic changes that may alter the cardiac output. These pathophysiological changes eventually cause oxidative stress. Granger *et al.* (6) found that oxidative stress was involved in the ischemia-reperfusion injury of the heart disease.

Oxidative stress produces excessive reactive oxygen species (ROS). In normal aerobic metabolism, the balance between oxidation and reduction is dynamically maintained. However, the imbalance between them may disrupt the antioxidant defense and lead to the excessive formation of ROS (7). At the same time, oxidative stress can selectively activate the pro-inflammatory pathways (8). ROS and inflammatory mediators can act together on myocardial subcellular structures such as proteins, nucleic acids, and mitochondria, causing myocardial metabolic dysfunction and structural changes. In the pro-inflammatory pathways, Ca<sup>2+</sup> is an important regulator of ROS production (9), and mitochondria is a known pool of calcium. The reduced Ca<sup>2+</sup> concentration in the mitochondria leads to a decreased ATP production, while the Ca<sup>2+</sup> overload in the mitochondria may cause excessive ROS production, resulting in a series of myocardial pathophysiological changes (10). Oxidative stress induced by intermittent hypoxia can induce endoplasmic reticulum stress by activating the angiotensin IIphospholipase C-trisphosphate (AngII-PLC-IP<sub>3</sub>) pathway, which induces the release of Ca<sup>2+</sup> from the endoplasmic reticulum into the cytosol and leads to  $Ca^{2+}$  imbalance (11).

The transient receptor potential canonical (TRPC) channel is a classical calcium channel widely distributed in mammalian cells, but the TRPC2 is not expressed in humans (12). In recent years, increasing attention has been paid to the physiological and pathological roles of TRPCs due to its wide expression (13). Some studies have found that the activation of TRPC channels is closely related to the occurrence and development of cardiovascular diseases. For example, TRPC1 is involved in the proliferation, migration and apoptosis of vascular smooth muscle cells (14-17); TRPC3 expression is associated with the hypertension (18), atrial fibrillation (19), arrhythmia, cardiomyocyte hypertrophy (20) and myocardial fibrosis (19). The expression of TRPC4 channel increases in the endothelial cells (21,22). TRPC6 is involved in the process of myocardial hypertrophy (20) and myocardial ischemiareperfusion injury (23). Recently, TRPC7 has been found to be also involved in the myocardial ischemiareperfusion injury (23). Thus, TRPCs are closely related to the pathogenesis of cardiovascular diseases including the OSAHS induced cardiovascular diseases. To investigate the role of TRPC in the pathogenesis of OSAHS, a rat model of OSAHS was established by intermittent hypoxic exposure, and the protein and mRNA expressions of TRPCs were detected in the heart by Western Blotting and qRT-PCR, respectively.

# **Methods**

# Animal model

This study was approved by the Ethics Committee of Xinjiang Medical University (IACUC-20170214045). Sprague Dawley rats (SD rats) were provided by the Experimental Animal Center of Xinjiang Medical University. Eighteen male SD rats, 15-17 w of age (at the time of surgery) were used in the present study. Animals were housed for 1 week before experiment and then randomly assigned to the experimental group (n=9) and the control group (n=9). In the experimental group, rats were placed in a chamber and exposed to intermittent hypoxia for 8 h (10AM-6PM) once daily. In the hypoxic exposure, rats were exposed to 8.5% oxygen for 1 min and then air (21% oxygen) for 1 min. Blood gas analysis was performed after 4 weeks (24,25): the arterial oxygen partial pressure was 20.9-29.7 mmHg, the blood oxygen saturation was 31.2-58.3%, and the blood oxygen partial pressure was 71.6 mmHg when they were exposed to air (21% oxygen). 106.4 mmHg, blood oxygen saturation was 92.2-97.4%, which was in line with the diagnostic criterion for human severe OSAHS (SaO<sub>2</sub> <80%). Among then, 1 rat in the experimental group and one rat in the control group died in the experiment. After hypoxic exposure, the rats were sacrificed and the hearts were harvested for detection of TRPC expressions.

# Real-time PCR relative quantitation of cardiomyocytes

The heart tissues (25-50 mg) were homogenized and total RNA extracted with 1 mL of Trizol. Then, 2 µL of RNA was reversely transcribed into cDNA, which served as templates for amplification. The primers used in the PCR were synthesized in the Ouyi Biotech Co., Ltd in Xinjiang Province (*Table 1*).

PCR was performed as follows: pre-denaturation at 95 °C for 2 min, 40 cycles of denaturation at 95 °C for 5 s, annealing at 60 °C for 30 s and extension at 60 °C for 30 s. The PCR products (10  $\mu$ L) were subjected to 1.8% agarose gel electrophoresis at 150 V for 10 min (26-28).

Table 1 Primers used for the amplification of TRPC get
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Primers	Sequences (5' to 3')	Size
TRPC1-F	CTGCTTATCTTCATGTGCGGTC	138 bp
TRPC1-R	GAAGCTGTGGTAGGCTCTGT	
TRPC3-F	ACGCAGTACGGCAACATC	209 bp
TRPC3-R	CGCACATAGCCTTTGCTGAT	
TRPC4-F	AAGGATTAGCTTCACGGGGTG	198 bp
TRPC4-R	CCTCCTCCTGGGCGTGTTTC	
TRPC5-F	CCATACAGAGACCGCATCCC	283 bp
TRPC5-R	CCTTGCGGATGGCATAGAGT	
TRPC6-F	AAACAGACTGACTCACCGGC	238 bp
TRPC6-R	CGCCAACTGTAGGGCATTCT	
TRPC7-F	TTGGGGAGCAACACCTTCAA	97 bp
TRPC7-R	TGAACATGTAGGCAGGACCC	
GAPDH-F	CAGGGCTGCCTTCTCTTGTG	172 bp
GAPDH-R	GATGGTGATGGGTTTCCCGT	

### Western blotting

The heart tissues were homogenized and lysed in 40 µL of RIPA with protease inhibitor (AR0105; Boster), and then the homogenate was centrifuged at 12,000 rpm for 15 min at 4 °C. The supernatant was collected, and the protein concentration was determined with BCA method (DQ111-01). Then, the proteins were mixed with 5× SDS-PAGE loading buffer (containing  $\beta$ -mercaptoethanol), and the mixture was boiled at 100 °C for 5 min to denatured proteins. Then, the mixture was centrifuged at 12,000 rpm for 5 min. The supernatant was collected and subjected to electrophoresis (12% separating gel and 5% stack gel, followed by protein transferring at 300 mA for 2 h. The membrane was blocked in 5% non-fat milk for 1 h at room temperature and then incubated with primary antibody at 4 °C over night (anti-rabbit TRPC6 (D3G1Q; 1:500; CST, anti-TRP 7 (N64A/36; 1:500, CST), anti-TRPC5 (1C8; 1:100, Santa cruz). The membrane was washed in TBS-T (PH 7.6) and then incubated with horseradish peroxidase conjugated secondary antibody, followed by visualization with enhanced chemiluminescence. The protein bands were scanned and analyzed with AlphaEaseFC 4.0 software. The expressions of TRPC1, TRPC3 and TRPC4 were undetectable, but the expressions of TRPC5, TRPC6 and TRPC7 were detectable.

#### Statistical analysis

Data are reported as mean  $\pm$  standard error (SEM). The statistical analysis was performed with SPSS version 19.0 (IBM). The independent sample T test for data with normal distribution and the rank sum test for data with abnormal distribution were used for comparisons between groups. A value of P<0.05 was considered statistically significant.

# **Results**

# mRNA expression of TRPC

The results in *Table 2* indicate that the ratio of RNA sample A260/A280 is an RNA purity test method, and RNA samples with a ratio ranging from 1.8 to 2.1 are considered acceptable. The sample of HVL213, HVL215, HVL216 of normal group and HVL201, HVL202, HVL203, HVL205, HVL206, HVL209 of test group were qualified. *Figure 1* shows that in the electrophoresis chart, 28S and 18S have higher brightness, 5S is weakest or no band, and the band is single intact, which is regarded as a qualified RNA sample. As shown in *Figure 2*, the expression of TRPC3, TRPC4, and TRPC5 in the OSAHS group was significantly higher than in the control group (P<0.05).

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No.	Sample grouping	Sample number	260 nm	280 nm	230 nm	260/280	260/230	C: ng/uL	Eligibility
1	Normal group	HVL213	5.44	2.96	6.51	1.84	0.84	217.49	Qualified
2		HVL216	1.86	1.03	1.34	1.80	1.39	74.45	Qualified
3	Test group	HVL201	6.96	3.57	4.56	1.95	1.53	278.58	Qualified
4		HVL202	5.43	2.87	5.32	1.89	1.02	217.24	Qualified
5		HVL203	7.28	3.72	4.56	1.96	1.60	291.30	Qualified
6		HVL205	6.04	3.15	4.36	1.92	1.39	241.58	Qualified
7		HVL206	7.27	3.71	6.12	1.96	1.19	290.90	Qualified
8		HVL209	8.96	4.64	6.37	1.93	1.41	358.54	Qualified
9	Normal group	HVL215	8.80	4.49	4.53	1.96	1.94	351.91	Qualified

Table 2 mRNA expression of different TRPC genes



Figure 1 RNA electropherogram.

#### Protein expression of TRPC by Western-blot

The protein sample concentration value was greater than 5.0  $\mu$ g/ $\mu$ L and the protein concentration is acceptable (*Table 3*). *Table 4* suggests that the expression of TRPC5 protein in the heart tissue of OSAHS rats was statistically significant (P<0.05) (*Figure 3*).

# Discussion

TRPC5 channel is one of TRPC channels. It is not only a non-selective cation channel with four specific structures, but also a non-voltage-gated cation channel mainly permeable to Ca<sup>2+</sup>. TRPC5 mainly regulates the permeability of microcirculation vessels to intracellular free Ca<sup>2+</sup> (29). The TRPC5 channel is mapped to q23 in the human X chromosome and mainly expressed in the central nervous system, kidney and cardiovascular system (30). The activation of TRPC5 channel via the phospholipase C (PLC) signaling pathway is its primary mechanism of action. Upon binding of the agonist to the G-protein coupled receptor or tyrosine receptor, the PLC is activated to hydrolyze phosphatidylinositol bisphosphate (PIP<sub>2</sub>) to produce inositol trisphosphate (IP<sub>3</sub>) and diacylglycerol (DAG), and then the DAG can be metabolized to arachidonic acid and linolenic acid. The IP<sub>3</sub> acts on the endoplasmic reticulum or sarcoplasmic reticulum causing Ca<sup>2+</sup> release in the calcium reservoir. When the calcium depletion is exhausted, the TRPC channel on the cell membrane is activated to initiate Ca<sup>2+</sup> influx. This is called calcium influx of the calcium reservoir manipulation, the loaded channel is store-operated Ca<sup>2+</sup> channel (SOCC), and TRPC5 channel is a kind of store-operated Ca<sup>2+</sup> channel (31). In recent years, some studies have focused on the role of TRPC5 channel in the pathogenesis of diseases of the kidney (32), tumor (33,34) and nerve (35,36). Studies have shown that TRPC5 channels are involved in the proliferation, contraction, migration, and hypertrophy of vascular smooth muscle cells (37).  $Ca^{2+}$  is an important regulator of ROS production, and Ca<sup>2+</sup> overload in the mitochondria can lead to excessive ROS production and cause a series of myocardial pathophysiological changes.

In this study, a rat model of OSAHS was established via intermittent hypoxia (IH) exposure, and the mRNA and protein expressions of different TRPCs were detected in



Figure 2 PCR primer identification electropherogram. \*, P<0.05.

Table 3 Prot	tein concenti	ration table	(part)
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Sample number	OD1	OD2	OD3	OD mean	OD blank	Post-dilution concentration (µg/mL)	Predilution concentration (µg/µL)
HV-L201	1.353	1.366	1.374	1.360	1.244	1287.778	12.878
HV-L202	1.528	1.540	1.552	1.534	1.418	1481.667	14.817
HV-L203	1.520	1.531	1.541	1.526	1.410	1472.222	14.722

Table 4 Western-blot analysis of protein expression in cardiac tissue of rats with obstructive sleep apnea syndrome (x+s, n=8)

Group	TRPC6	TRPC7	TRPC5
Normal group	1.460±0.537	6.030±0.675	6.822±1.909
Test group	1.530±0.767	5.028±1.836	11.448±2.601
Т	-0.137	0.886	-2.648
Ρ	0.896	0.410	0.038



Figure 3 Expression of TRPC5 protein in the heart tissue of OSAHS rats.

the heart.

Results showed the mRNA expression of TRPC3 (normal group  $1.002\pm0.080$ , experimental group  $1.576\pm0.218$ ), TRPC4 (normal group  $1.003\pm0.092$ , experimental group  $1.167\pm0.063$ ), and TRPC5 (normal group  $1.001\pm0.055$ , experimental group $1.198\pm0.102$ ) in the heart tissues of OSAHS group was significantly higher than in the control group (P<0.05). This suggests that the intermittent hypoxia may affect the mRNA expression of TRPC3/TRPC4/TRPC5 in rat heart.

Furthermore, the protein expression of different TRPCs was also detected in the heart tissues of rats after intermittent hypoxia exposure. The protein expression of TRPC1/TRPC3/TRPC4 was undetectable in two groups, but that of TRPC5/TRPC6/TRPC7 was detectable in both groups. Our results showed the protein expression of TRPC5 in the heart of the OSAHS group was significantly different between two groups (P<0.05), while the protein expression of TRPC6/TRPC7 was comparable between them. Compared with the control group, the protein expression of TRPC5 in the heart increased dramatically in

the OSAHS group. This indicates that TRPC5 channel is likely to be involved in the myocardial pathophysiological changes caused by OSAHS (intermittent hypoxia), but the specific mechanism underlying the role of TRPC5 in the OSAHS is needed to be further studied, which would provide a new target for the clinical prevention and treatment of OSAHS related cardiac damage.

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# Footnote

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/apm.2020.04.08). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Xinjiang Medical University (IACUC-20170214045).

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