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Experimental Research Article

Hypoxia-Induced Impairment of Glucose Homeostasis: Sympathovagal Imbalance and the Potential Therapeutic Role of L/N type Calcium Channel Blocker Cilnidipine

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ABSTRACT

Introduction: Frequent occurrence of diabetes mellitus type 2 (T2DM) in patients with respiratory disease suggests a role of underlying chronic hypoxia (CH) in its pathogenesis. The present study aimed to delineate the link between CH, sympathovagal balance, and glucose homeostasis (GH) as well as to explore the role of L/N type calcium channel blocker, cilnidipine in alleviating CH-induced pathophysiology in experimental animals.

Methods: Wister rats were divided into four groups: group I: control, (normoxia, 21%O2); group II: chronic hypoxia (CH) (10%O2, 90%N2); group III: normoxia+cilnidipine (cil, 2mg/kg/day); group IV: CH+Cil (10%O2, 90%N2 + cil, 2mg/kg/day). Sympathovagal balance was assessed by heart rate variability (HRV) analysis. Glucose homeostasis was evaluated by fasting plasma glucose (FPG), fasting plasma insulin, oral glucose tolerance test (OGTT), HOMA-IR, and HOMA-β. The fasting lipid profile was also assessed.

Results: CH increased LF (nu), LF/HF, and decreased HF (nu). Additionally, CH increased FPG and HOMA-IR which were positively correlated with LF/HF and induced an atherogenic lipid profile. OGTT revealed normal 2h post-challenge glucose levels. In the cilnidipine-treated CH exposed group, LF (nu), HF (nu), and LF/HF were lower compared CH and glucose homeostasis parameters were comparable to control.

Conclusion: CH, by enhancing sympathetic activity, disturbs glucose homeostasis, leading to isolated impaired fasting glycemia (i-IFG), a prediabetic state. Cilnidipine improved glucose homeostasis in CH-exposed experimental animals by ameliorating sympathetic hyperactivity with complementary effects on lipid profile, suggesting its utility as an adjunctive therapy against CH-induced T2DM.

Keywords:
Cilnidipine
HOMA IR
Hypoxia
Glucose Tolerance Test
Prediabetes

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Introduction

The prevalence of diabetes is influenced by complex interactions between genetic, metabolic, and environmental factors (Galicia-Garcia et al., 2020). Studies have reported a more frequent occurrence of diabetes mellitus type 2 (T2DM) in patients with respiratory disease when compared to the general public, with 2-37% of those with chronic obstructive pulmonary disease (COPD) reported to develop DM in due course (Rogliani et al., 2014; Rogliani et al., 2015; Cazzola et al., 2010; Lee et al., 2013; Mahishale et al., 2015; Cavaillès et al., 2013). Chronic hypoxia (CH) underlies respiratory diseases, including COPD (Lewis et al., 2015; Ramirez et al., 2012). Probably, hypoxia has a likely role in the pathophysiology of T2DM in patients with respiratory illnesses, like COPD. CH causes sympathovagal imbalance characterized by elevated sympathetic activity mediated by chemoreceptor reflexes and changed baroreceptor function (Bagali et al., 2020; Hainsworth et al., 2007). Elevated sympathetic drive and diminished vagal efferent function underlie the multisystemic pathophysiology of T2D, including reduced insulin secretion, gastroparesis, hypertension, and high cardiovascular mortality (Yang, 2013). Insulin resistance is strongly associated with sympathovagal imbalance. One of the main characteristics of insulin resistance disorders is impaired skeletal muscle glucose absorption. Long-term sympathetic hyperactivity can reduce skeletal muscle blood flow, decreasing post-prandial glucose uptake. It also stimulates additional insulin secretion by the pancreas, leading to insulin resistance (Thorp and Schlaich, 2015). There is a paucity of information regarding the effects of CH on glucose homeostasis particularly in the background of potential alterations in the sympathovagal balance caused by CH.

Given the predominant role of sympathetic hyperactivity in the pathophysiology of DM, drugs that modulate sympathetic neurotransmission have the potential to alleviate its detrimental effects on glucose homeostasis. Cilnidipine, a calcium channel blocker (CCB) is a widely used antihypertensive. Owing to its unique pharmacological profile of blocking sympathetic N-type calcium channels in addition to vascular L-type calcium channels, cilnidipine can impact sympathetic neurotransmission thereby influencing glucose homeostasis. Thus, cilnidipine can be a prospective drug for use as an additional therapy in patients experiencing chronic hypoxia, to prevent or postpone the occurrence of T2DM in patients with respiratory diseases like COPD.

Hence, the present study aimed to evaluate glucose homeostasis in chronic sustained hypoxia considering the interplay with sympathovagal balance. The study also evaluated the impact of cilnidipine, a dual L/N type CCB, on these parameters in experimental rats. We hypothesize that exposure to CH impairs sympathovagal balance, which in turn impairs glucose homeostasis. We also hypothesize that administration of cilnidipine, a dual L/N type CCB, improves CH-induced impaired glucose homeostasis by reducing sympathetic neurotransmission.

Materials and Methods

Ethics approval

Ethical approval for the study was obtained from Institutional Animal Ethics Committee (IAEC). The animal care guidelines issued by the Committee for the Purpose and Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests (Animal Welfare Division), Government of India were strictly adhered to throughout the study.

Experimental animals

24 male Wister strain albino rats from the institution's animal house, 8-10 weeks old and weighing 180-250 g were included in the study. The experimental animals were maintained in the conventional settings with a temperature range of 22-24°C and a 12-hour light/12-hour dark cycle with food and water *ad libitum*.

Study Design

The animals under study (n=24) were randomly categorized into four groups (table 1). The animals in each group were matched for body weight. The duration of the intervention was 21 days. During the intervention period, the daily food consumption of each rat was monitored.

Exposure to Chronic Hypoxia (CH)

Rats in cages (4/cage) were placed in an acrylic chamber (300 L). The animals under study were exposed to 90% nitrogen (N_2) and 10% inspired oxygen (O_2). The granules of soda-lime were used to remove CO_2 and the desiccator maintained humidity. The cages were cleaned twice a week, and food and water were replaced. The

TABLE 1: Allocation of experimental animals into groups

Sl. No	Groups	Intervention
	Group I (Control)	Normoxia + vehicle by oral gavage
	Group II (CH)	Chronic hypoxia + vehicle by oral gavage
	Group III (Cil)	Cilnidipine 2.0 mg/kg/day in vehicle by oral gavage
	Group IV (CH + Cil)	Chronic hypoxia + Cilnidipine 2.0 mg/kg/day in vehicle by oral gavage

experimental animals (groups II and IV) were exposed to hypoxia for 21 days (Das et al., 2015).

Administration of Cilnidipine

The dose of cilnidipine (Laksh Finechem, Pvt. Ltd, Gujarat, India) to be administered was calculated as 2.0 mg/kg/day (Nair and Jacob, 2016). Due to its poor water solubility, cilnidipine was suspended in the vehicle [sodium carboxy methyl cellulose (Na CMC) 0.5%]. The suspension was freshly made every morning and administered by oral gavage for 21 consecutive days (Bagali et al., 2020).

Gravimetry

The body weight of rats was measured using an electronic scale (Practum 1102-10IN, Germany) on day 0 of the experiment (starting body weight) and the day following 21 days of intervention (day 22, final body weight) (the intervention period was 21 days, i.e. from day 1-day 21). At the start of the experimental protocol, the rats in each group were matched for body weight.

Change in body weight in % was computed with the following formula.

$$\text{Change in body weight (\%)} = \frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}} \times 100$$

Assessment of sympathovagal balance

Sympathovagal balance was assessed by heart rate variability (HRV) analysis. ECG was recorded using needle subcutaneous electrodes using Biopac Student Lab 4.1 software in the morning following overnight fasting. The rats were administered with ketamine (60mg/kg, i.p) and xylazine (6mg/kg, i.p). A 5-minute ECG was recorded in anesthetized rats in dorsal recumbency by inserting the needle electrodes in the right (negative) and left (positive) front legs and right rear leg (GND). The ECG was examined offline for artifacts followed by manual removal of ectopic beats. For HRV analysis, RR intervals were extracted and exported to Kubios software version 2.0 (developed by the Department of Physics, University of Kuopio, Finland) (Reddy et al., 2020). HRV analysis is a widely used non-invasive approach to assess sympathetic, and parasympathetic activity as well as sympathovagal balance. HRV analysis involves time and frequency domain indices. Frequency domain analysis of RR interval oscillations uses two major frequency bands a) low frequency (LF) band (0.04-0.15Hz) predominantly reflects sympathetic activity b) High frequency (HF) (0.15-0.4 Hz) band denotes the parasympathetic activity. LF/HF ratio is used to determine cardiac sympathovagal balance (Shaffer and Ginsberg, 2017).

Assessment of Glucose Homeostasis

After an intervention period of 21 days, glucose homeostasis was evaluated in all the experimental animals.

1. Estimation of Fasting Plasma Glucose (FPG): After the last day of intervention, the experimental animals were fasted overnight. For fasting blood glucose estimation, blood was collected the next morning from the tail vein. Glucose was estimated using a commercial kit (ERBA diagnostics, Mannheim GmBH) according to the manufacturer's protocol.

2. Estimation of Fasting Plasma Insulin (FPI): Rat Insulin ELISA kit (Catalog No: BEK1243, Chongqing Biospes Co., Ltd, Chongqing, China) was used to estimate insulin, as per the protocol in the product manual in overnight fasted rats.

3. Calculation of HOMA-IR: HOMA-IR (Homeostasis Model Assessment of Insulin Resistance), which largely represents hepatic insulin resistance was estimated using the following formula (Faerch et al., 2009; Das et al., 2016).

HOMA-IR = fasting plasma insulin (milliunits/L) x fasting plasma glucose (millimoles/L) /22.5

4. Calculation of HOMA-β: HOMA-β an estimate of β-cell function and an index of insulin secretory function was estimated using the following formula (Khalil

et al., 2023; Yoon et al., 2016)

HOMA- β = 20X fasting insulin (μU/ml)/[fasting plasma glucose (mg/dl)-63]

5. Oral Glucose Tolerance Test (OGTT): On the day after the last day of intervention, OGTT was done (day 22, intervention period day1-day 21). The rats were fasted overnight after the last day of intervention. OGTT was carried out in the morning. The experimental rats were challenged with a glucose load of 2.0 g/kg (20% solution of glucose) administered by oral gavage. Glucose levels were estimated in tail-snip blood with a handheld glucometer (ACCU-CHEK Active; Roche) at 0, and subsequently at 30, 60, 90, and 120 min after glucose load (Abu Eid et al., 2018; Bowe et al., 2014; Polak et al., 2013).

Assessment of plasma lipid profile

The plasma lipid profile was assessed on day 22 of the experimental protocol. Total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) were analyzed using the commercial diagnostic kit (Tranasia Bio-medicals Ltd, ERBA Diagnostics, Mannheim GmBH). The Friedwald formula was used to calculate low density lipoprotein (LDL) and very low density lipoprotein (VLDL) (Friedwald et al., 1972) as indicated below:

LDL (mg/dl) = Total cholesterol – HDL cholesterol - TG/5

VLDL= TG/5

Statistical Analysis

Statistical analysis was done with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Data is represented as mean ± standard deviation. One-way ANOVA was employed to test for statistical significance across groups, followed by Tukey's *post hoc* test to ascertain significant intergroup differences. Pearson's correlation was used to assess the association between the two variables. For statistical significance, $P < 0.05$ was considered.

Results

Gravimetry

Table 2 shows the comparison of initial body weight (Day 0), final body weight (Day 22), and % body weight gain both within groups and between groups. Before the start of the experimental protocol, the rats were matched for body weight. There was a significant increase in mean body weight in rats of all groups after the intervention period of 21 days (p=0.000 for all groups on paired t-test). One-way ANOVA revealed significant (p=0.000) differences in the post-intervention body weight (day 22) between groups, indicating a non-uniform increase in body weight across groups. % body weight gain was significantly (p=0.000) different between groups with lesser gain in group II (CH) and group IV (CH+Cil) compared to group I (control). On comparing group II (CH) and group IV (CH+Cil), a lower % body weight gain was observed in group II.

TABLE 2: Body weight comparison between groups

Variable	Group I (Control)	Group II (CH)	Group III (Cil)	Group IV (CH+Cil)	ANOVA F	ANOVA *P*
Starting body wt (g, Day 1)	194.833±3.43 [a]	197.50±4.63 [a]	203.00±9.59 [a]	196.00±6.35 [a]	1.89	0.164
Final body wt (g, Day 22)	246.80±6.23 [a]	219.74+6.97[b]	257.57±11.71[a]	223.57±6.79[b]	29.45	0.000*
% body wt gain	26.66±1.11[a]	11.25±1.83 [b]	26.89±1.46[a]	14.08±1.63[c]	172.26	0.000*

Superscripts a, b, c indicate significant difference between groups. *$P \leq 0.05$. Wt: weight, n=6 per group. Post intervention (day 22) body weight and % body weight gain was significantly different between groups.

TABLE 3: Heart rate variability measures across groups

Variable	Group I (Control)	Group II (CH)	Group III (Cil)	Group IV (CH+Cil)	ANOVA F value	ANOVA *P*-value
LF (nu)	47.45±4.11 [a]	63.34±2.83[b]	34.48±3.01[c]	55.14±2.86[d]	85.43	0.000*
HF (nu)	56.63±3.09 [a]	37.55±3.47[b]	57.15±3.15[a]	49.02±3.57[c]	45.26	0.000*
LF/HF	0.85±0.03[a]	1.70±0.17[b]	0.61±0.07[c]	1.03±0.23[a]	169.51	0.000*

Superscripts a, b, c, d indicates significant difference between groups. *$P \leq 0.05$. n=6/group. LF (nu), HF (nu), and LF/HF were significantly different between groups.

HRV analysis

The frequency domain measures of HRV are compared in Table 3. One-way ANOVA revealed significant (p=0.000) differences in LF (nu), HF (nu), and LF/HF between groups. LF (nu) was higher in group II (CH) and group IV (CH+Cil) compared to group I (control) with a greater increase in the former. HF (nu) was lower in group II (CH) and group IV (CH+Cil) compared to group I (control) with a greater decrease in the former.

Lipid Profile

The lipid profile was compared among groups, as presented in Table 4. In group II (CH), total cholesterol, triglycerides, HDL, LDL, and HDL/LDL were increased compared to group I (control). A statistically insignificant increase in VLDL in group II (CH) was also noted. In group IV (CH+Cil), all the lipid profile parameters were lower while HDL/LDL was higher when compared to group II (CH) but not statistically significant (p=0.09).

Assessment of GH

Table 5 depicts a comparison of fasting plasma glucose, fasting plasma insulin, HOMA-IR and HOMA-β among groups.

Fasting plasma glucose

Group II (CH) had higher fasting plasma glucose compared to group I (control). In Group IV (CH+Cil), fasting plasma glucose levels were comparable to those in Group I and significantly lower than in Group II (CH).

Fasting plasma insulin

No significant (p=0.26) differences in fasting plasma insulin were noted among the groups.

HOMA-IR

HOMA-IR in groups I (control), III (Cil), and IV (CH+Cil) was comparable, but significantly higher in group II (CH).

HOMA- β

HOMA- β in groups I (control), III (Cil), and IV (CH+Cil) was comparable, but significantly lower in group II (CH). Post-hoc analysis showed lower HOMA-β in group II (CH) vs. group III (cil) (p=0.004)

TABLE 4: Comparison of lipid profile among groups (n=6/group)

Parameters	Group I (Control)	Group II (CH)	Group III (Cil)	Group IV (CH+-Cil)	ANOVA	
					F value	*P* value
Total Cholesterol	63.93±3.43[a]	73.00±5.51[b]	60.98±3.60[a]	68.33±2.73[b]	10.549	0.000*
Triglycerides	53.83±5.87[a]	66.66±571[b]	56±4.85[a]	60±3.16[a]	7.570	0.001*
HDL	33.29±4.27[a]	26.83±3.81[b]	32±3.84[a]	29.16±3.76[a]	3.25	0.043*
LDL	26.01±4.38[a]	33.16±2.63[b]	24±4.93[a]	28.78±5.13[a]	4.90	0.01*
VLDL	10.56±2.38[a]	14.00±3.36[a]	10.86±1.45[a]	12.83±3.45[a]	2.06	0.137
HDL/LDL	1.31±.27[a]	0.81±0.12[b]	1.36±0.25[a]	1.03±0.18[a]	8.398	0.001*

Superscripts a and b indicate significant difference between groups. *$P \leq 0.05$. n=6 per group. Total cholesterol, triglycerides, HDL, LDL, and HDL/LDL were significantly different between groups.

TABLE 5: Glucose homeostasis compared between groups

Parameters	Group I (Control)	Group II (CH)	Group III (Cil)	Group IV (CH+Cil)	ANOVA	
					F value	*P* value
Fasting plasma glucose mg/dl)	93.5± 6.75[a]	107.75± 6.75[b]	85.33± 3.81[a]	93.50±3.10[a]	10.421	0.002*
Fasting plasma Insulin (mIU/L)	28.77± 1.26[a]	30.88 ± 2.91[a]	28.29 ±1.29[a]	29.02 ± 1.36[a]	1.509	0.262
HOMA-IR	7.0 ± 0.16[a]	8.46±0.20[b]	6.55±0.45[a]	6.02±0.75[a]	20.69	0.000*
HOMA-β	19.71±5.33[a]	14.05±2.67[b]	25.83±4.02[a]	19.16±1.94[a]	6.68	0.007*

Superscripts a and b indicate significant differences between groups. *$P \leq 0.05$. n=6 per group. Fasting plasma glucose, HOMA IR, and HOMA- β were significantly different between groups.

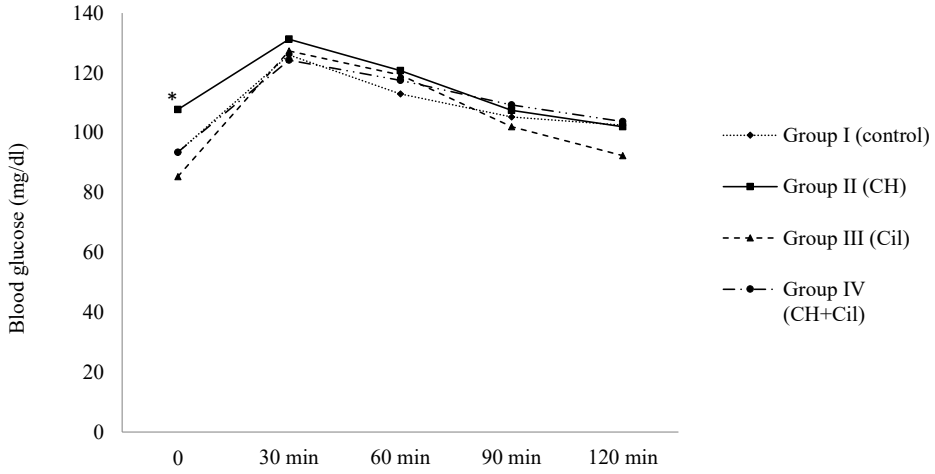

FIGURE 1. Comparison of plasma glucose concentrations during OGTT between the study groups. The figure presents the time course of blood glucose after an oral glucose challenge of 2g/kg b.wt. administered by oral gavage after 21 days of chronic hypoxia exposure. Except for the higher fasting blood glucose (0 min) in group II (CH), the time course of blood glucose after an oral glucose challenge and 2 h post-challenge blood glucose were comparable among groups n=6/group. *Significantly higher fasting blood glucose in group II.

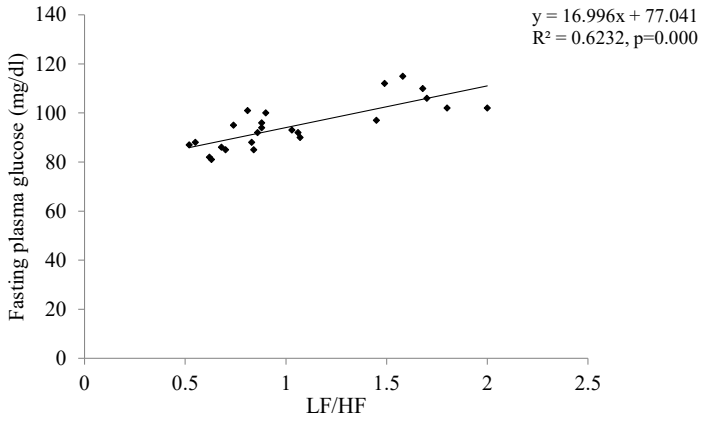

FIGURE 2. Correlation between fasting plasma glucose and LF/HF. Pearson's correlation was done to determine the correlation between measures of glucose homeostasis and sympathovagal balance (LF/HF). Fasting plasma glucose and LF/HF are positively correlated (R=0.790, P=0.000) (n=6/group).

OGTT

A comparison of plasma glucose concentrations during OGTT among groups is presented in Fig. 1. After 21 days of CH, group II (CH) had significantly (p=0.017) higher fasting blood glucose (0 min) than group I (control). However, in group IV (CH+Cil) fasting blood glucose levels were comparable to group I (control). The time course of blood glucose after an oral glucose challenge and 2 h post-challenge blood glucose were comparable among groups.

Correlation of GH and measures of HRV (LF/HF ratio)

Pearson's correlation was done to determine the correlation between measures of GH and LF/HF.

Fasting plasma glucose and LF/HF are positively correlated (R=0.790, *P*=0.000) as depicted in Fig. 2.

HOMA-IR and LF/HF are positively correlated (R=0.656, *P*=0.001) as seen in Fig. 3.

Discussion

COPD is a significant risk factor for the development and/or progression of T2DM. Despite the fact that COPD and T2DM are two separate clinical entities, there may be a pathophysiological relationship between the two chronic conditions (Glaser et al., 2015). In respiratory diseases including COPD, chronic sustained hypoxia is a predominant feature (Lewis et al., 2015) which possi-

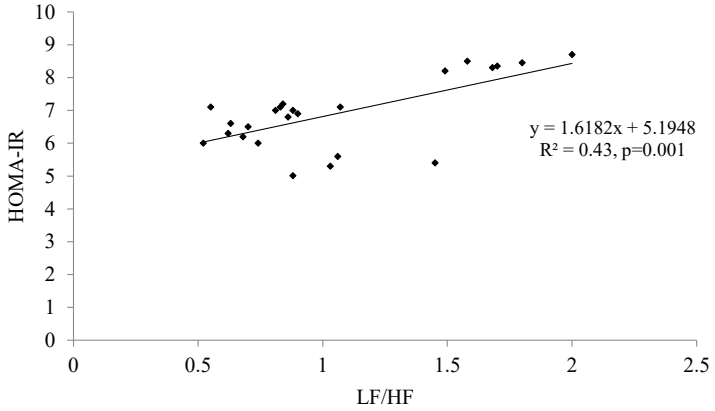

FIGURE 3. Correlation between HOMA-IR and LF/HF. Pearson's correlation was done to determine the correlation between measures of glucose homeostasis and sympathovagal balance (LF/HF). HOMA-IR and LF/HF are positively correlated (R=0.656, P=0.001) (n=6/group).

bly signals a repertoire of events that disrupt glucose homeostasis, paving the way for the onset of T2DM. This study was done to characterize the association between chronic sustained hypoxia, sympathovagal balance, and glucose homeostasis. The study also explored the role of cilnidipine, a CCB that blocks both L and N-type calcium channels, on glucose regulatory mechanisms during CH-induced altered sympathovagal balance.

Despite an increase in body weight in all the experimental animals, body weight gain was not uniform across groups. The lower body weight gain (%) on CH exposure may be due to higher metabolism and energy expenditure (Fenik et al., 2012). The autonomic nervous system also influences body weight by controlling energy expenditure, especially sympathetic activation increases energy expenditure that in turn reduces body weight (Messina et al., 2013). In our study, non-uniform body weight gain indicates altered functions of the autonomic nervous system. Interestingly, the cilnidipine-treated CH-exposed group (group IV) demonstrated an improvement in body weight gain (%) when compared to CH-exposed animals (group II).

Frequency domain measures of HRV analysis revealed elevated sympathetic activity, reduced parasympathetic activity, and a shift in the sympathovagal balance towards sympathetic hyperactivity on CH exposure (group II). Exposure to hypoxia elicits sympathetic hyperactivity that could be mediated either by stimulation of peripheral chemoreceptors or activation of oxygen-sensitive cells in the brain stem (Xie et al., 2001).

On CH exposure, FPG was increased with normal FPI, high HOMA IR, and normal 2h post-challenge blood glucose levels. In the present study, the combination of elevated fasting glucose level without a compensatory increase in fasting insulin, a greater HOMA IR, and a lower HOMA-β indicated a reduced pancreatic β-cell response to glucose-driven insulin secretion and hepatic insulin resistance (i.e. diminished suppressive effect of insulin on hepatic glucose production) (Abu Eid et al., 2018; Gutch et al., 2015). Hence, CH exposure resulted in isolated impaired fasting glycemia (i-IFG) with concomitant insulin resistance (reflected by HOMA IR) and β cell dysfunction. Further, the positive correlation of FBS and HOMA IR with low-to-high frequency (LF/HF) ratio is supportive of the role of sympathetic overactivity in inducing elevation of fasting blood glucose and insulin resistance. In the fasting state, hepatic glucose production is believed to be the major determinant of glucose homeostasis (Abu Eid et al., 2018). On chronic sustained hypoxia exposure, increased fasting glucose level is the likely outcome of an increase in hepatic glucose production mediated by sympathetic hyperactivity. In the fasted state, the sympathetic nervous system (SNS) increases hepatic glucose output by accelerating gluconeogenesis (Nonogaki, 2000). Sympathetic activation causes the release of catecholamines from the adrenal medulla, which in turn promotes glucose production by the liver (Thorp and Schlaich, 2015). Additionally, stimulation of splanchnic sympathetic nerves to the pancreas causes glucagon secretion via β-adrenergic receptors on islet cells and suppresses insulin secretion via α-adrenergic receptors (Thorp and Schlaich, 2015). Besides the liver and pancreas, sympathetic stimulation also affects skeletal muscle glucose metabolism induc-

ing glycogenolysis by β-adrenergic receptor activation releasing lactate into circulation. Lactate is directed to the liver for further hepatic gluconeogenesis. Thus, SNS increases fasting blood glucose through its actions on the liver, pancreas, and skeletal muscle either individually or in combination (Nonogaki, 2000). CH is a stressor that activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of catecholamines via the SNS and glucocorticoids via the adrenal gland. Catecholamines and glucocorticoids promote glucose production by the liver and impair insulin sensitivity in peripheral tissues (Thorp and Schlaich, 2015; Herman et al., 2016; Hinds and Sanchez, 2022). CH-exposed experimental animals displayed an atherogenic pattern of lipid profile characterized by higher triglycerides, total cholesterol, LDL, HDL/LDL ratio, and decreased HDL. This lipid abnormality is further associated with the risk of T2DM (Safari et al., 2020). Insulin resistance can cause dyslipidemia by impairing lipid metabolism. Further diabetic dyslipidemia frequently occurs several years before type 2 diabetes, implying that impaired lipid metabolism is an early event in the development of CVD in type 2 diabetes (Parhofer, 2015; Ormazabal et al., 2018).

Improved glucose homeostasis and HRV analysis depicting favorable sympathetic activity and sympathovagal balance in cilnidipine-treated hypoxic rats are suggestive of ameliorating effects of cilnidipine on impaired glucose homeostasis probably by reducing the hypoxia-induced enhanced sympathetic drive. These actions of cilnidipine are probably mediated by its sympathetic N-type calcium channel-blocking actions in addition to the vascular L-type calcium channels. N-type calcium channels are located on the sympathetic nerve terminals and mediate sympathetic neurotransmission. Cilnidipine blocks N-type calcium channels reducing sympathetic neurotransmission consequently lowering the hypoxia-induced enhanced sympathetic drive and ward off the impaired glucose homeostasis (Takahara et al., 2002; Takahara, 2009). The impact of hypoxia and sympathetic hyperactivity on the hypothalamo pituitary adrenal (HPA) axis has not been assessed which is the limitation of the current study.

Conclusion

The findings of the study provide a basis for understanding the link between CH, sympathetic hyperactivity, and glucose homeostasis. Chronic sustained exposure to hypoxia is likely to induce isolated impaired fasting glycemia (i-IFG), a prediabetic state characterized by abnormal fasting glucose levels with normal 2h post-challenge plasma glucose. Over time, this prediabetic state can progress to T2DM. The abnormalities in the lipid profile further increase the risk of T2DM. Hence, patients with respiratory diseases should be closely monitored for alterations in glucose homeostasis and subsequent development of T2DM. Cilnidipine improved glucose homeostasis in experimental animals subjected to CH by reducing sympathetic overactivity. Hence, cilnidipine could be utilized as an additional therapy in patients experiencing hypoxia to prevent/delay DM onset. However, additional studies are needed to prove the impact of cilnidipine on improving diabetes outcomes.

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