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Impaired hypoxic cerebral vasodilation in younger adults with metabolic syndrome

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Abstract

Metabolic syndrome (MetSyn) increases the risk of cerebrovascular disease and stroke; however, its impact on human cerebral circulation remains unclear. Reduced cerebral dilation is also associated with an increased risk of stroke and may occur in MetSyn adults. We hypothesised that MetSyn adults would exhibit reduced cerebral vasodilation to hypoxia and hypercapnia. Middle cerebral artery velocity (MCAv) was insonated with Doppler ultrasound in younger (approximately 35 years) MetSyn and healthy adults. We measured mean arterial blood pressure (MABP), arterial oxygen saturation (S_pO_2) and end tidal carbon dioxide (P_{ETCO_2}). Cerebrovascular conductance index (CVCi) was calculated as $MCAv \times 100 / MABP$. Cerebral vasodilation ($\Delta CVCi$) to hypoxia ($S_pO_2 = 90\%$ and 80%) and hypercapnia ($+10$ mm Hg P_{ETCO_2}) was assessed. Baseline MCAv was similar, while adults with MetSyn had lower baseline CVCi. MetSyn adults demonstrated markedly reduced $\Delta CVCi$ compared to healthy adults in response to hypoxia ($90\% S_pO_2$: 1 ± 2 vs 6 ± 2 ; $80\% S_pO_2$: 5 ± 2 vs 15 ± 3 cm/s/mmHg, $p < 0.05$). Both groups demonstrated similar $\Delta CVCi$ to hypercapnia (18 ± 2 vs 20 ± 2 cm/s/mmHg). These data are the first to demonstrate that younger MetSyn adults have impaired hypoxia-mediated cerebral vasodilation prior to clinically overt cerebrovascular disease. These findings provide novel insight into cerebrovascular disease onset in MetSyn adults.

Keywords

Cerebral blood flow; transcranial Doppler; risk factors

Introduction

Metabolic syndrome (MetSyn) is a multi-component condition that increases an individual's relative risk of developing cardiovascular disease,^{1–3} including stroke.⁴ However, the impact of MetSyn on human cerebral vessel function has not been examined.

Proper cerebral blood flow regulation is critical for maintaining the homeostatic environment of the brain. Blunted dilation (cerebrovascular reactivity) to challenges such as hypoxia or hypercapnia is associated with an increased risk of stroke.^{5–7} Dilation to hypoxia or hypercapnia is clinically important, as these stimuli occur in sleep disordered breathing and acute ischaemic stroke.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Given the elevated incidence⁴ and possible severity⁸ of stroke in MetSyn, it is important to understand cerebrovascular pathophysiology to reduce the risk, incidence and severity of stroke in this rapidly expanding population. No literature has addressed the key gap in knowledge of whether impaired vascular regulation is present prior to the clinical manifestation of disease. In older adults with atherosclerosis, MetSyn is an independent predictor of impaired cerebral dilation,⁹ a finding that is not surprising given the combination of advanced age and presence of disease. In contrast, virtually nothing is known about the onset and progression of cerebrovascular disease in younger adults with MetSyn. Early detection of vascular dysfunction could allow for medical and lifestyle interventions to slow or reverse disease progression and have important benefits for stroke outcomes.

The purpose of this study was to test the hypothesis that younger adults with MetSyn would display blunted cerebral vasodilator responses during hypoxia and hypercapnia compared to healthy controls. We studied younger adults to investigate the influence of MetSyn on cerebrovascular function prior to the onset of clinically overt metabolic and cardiovascular disease.

Methods

Subjects

Nine adults with metabolic syndrome (MetSyn, 37±3 years, two female) and ten healthy adults (32±2 years, four female) participated in this study. Health history and physical activity were assessed by questionnaires. Subjects were not taking any cardiovascular medications and were free of cardiovascular, cerebrovascular, metabolic, pulmonary and neurologic disease. One subject with MetSyn reported sleep-disordered breathing. All subjects were sedentary (<60 minutes of moderate-intensity aerobic exercise per week) and did not use any tobacco. Females had a regular menstrual cycle (oral contraception allowed), were studied during the early follicular phase of their menstrual cycle (day 1–5) and were not pregnant (urine test). Subjects reported to the laboratory after fasting for 10 hours and abstaining from heavy exercise, alcohol, caffeine and NSAIDs for 24 hours.

Adults with MetSyn were categorised based on the NCEP-ATP III definition of MetSyn, as modified by the American Diabetes Association and International Diabetes Federation.¹ Healthy controls were lean, normotensive, normolipidaemic and normoglycaemic. All procedures performed for this project obeyed the Declaration of Helsinki and were approved by the University of Wisconsin-Madison Institutional Review Board. Written informed consent was obtained from each subject.

Measurements

Height and weight were measured and body mass index (BMI) (kg/m²) was calculated. Venous blood was analysed for glucose and lipids for confirmation of MetSyn. Subjects were instrumented for continuous monitoring with a 3-lead electrocardiogram (heart rate, HR), automatic sphygmomanometer (mean arterial blood pressure, MABP) and pulse oximeter (arterial oxygen saturation, S_pO₂) (Datex-Ohmeda, Helsinki, Finland).

Middle cerebral artery blood velocity (MCAv) was collected using a 2 MHz probe (Neurovision model 500M, Multigon Industries, Inc., Yonkers, New York, USA) placed in the temporal window using standard search criteria.¹⁰ The Doppler probe was held in place by an adjustable head-band. Minute ventilation (V_E) and inspired oxygen fraction were measured with a metabolic cart (MedGraphics, Ultima PFX, St. Paul, Minnesota, USA). End-tidal carbon dioxide (P_{ET}CO₂) was measured breath-by-breath with a CO₂ analyser

(Ametek, S-3A/I and CD-3A, Berwyn, Pennsylvania, USA) as a reliable surrogate of arterial CO₂ content.¹¹

Protocol

Hypoxia and hypercapnia trials were performed in randomised order with the subjects in a semi-recumbent position. Each hypoxia and hypercapnia trial was followed by ten minutes of room air breathing, providing sufficient time for all variables to return to baseline levels.

Isocapnic hypoxia was achieved by subjects breathing through a mouthpiece while nasal air flow was occluded. The mouthpiece was attached to a two-way non-rebreathing valve (2700 Series, Hans Rudolph Inc., Kansas City, Missouri, USA) connected to a gas mixer to control inspired air composition. Following five minutes of room air breathing, inspired oxygen was titrated to maintain five minutes of steady state S_pO₂ at 90% followed by transition to five minutes of S_pO₂ at 80%. To isolate the effects of hypoxia, baseline P_{ET}CO₂ was maintained throughout the trial by adding CO₂ to the blended hypoxic gas. Hypoxia trials were performed in duplicate and results were averaged for analysis.

Hyperoxic hypercapnia was performed by subjects breathing through a mouthpiece connected to a three-way sliding valve (Model 2870, Hans Rudolph Inc., Kansas City, Missouri, USA) while wearing a nose clip. The mouthpiece was connected to a meteorological balloon filled with a hyperoxic (to isolate the effects of hypercapnia), hypercapnic mix of gas (CO₂=3%, O₂= 40%, N₂=57%) to a volume one litre above predicted vital capacity based on age and height. After five minutes of room air breathing, subjects began to rebreath air from the balloon. Trials were terminated when the subject's P_{ET}CO₂ reached 10 mm Hg above eupnea (about two minutes). Hypercapnia trials were performed in triplicate and results were averaged for analysis.

Data analysis

Data were recorded using PowerLab suite (ADInstruments, Colorado Springs, Colorado, USA). The last 30 seconds of baseline and steady state data from each hypoxia level were averaged from each trial. For hypercapnia trials, the last 30 seconds of baseline data and the last 10 seconds of hypercapnia were averaged to examine the peak response to the stimulus.

MCAv values were normalised for perfusion pressure and are presented as cardiovascular conductance indices (CVCi = MCAv*100/MABP). Cerebral vasodilation was defined as a positive change of CVCi (Δ CVCi) from baseline, since a change of conductance has a predictable relationship with vasodilation.¹² Vascular reactivity slopes to hypoxia and hypercapnia were calculated as Δ CVCi/ Δ S_pO₂ and Δ CVCi/ Δ P_{ET}CO₂.¹³

Minitab 15 (State College, Pennsylvania, USA) was used for statistical analysis. Subject characteristics were compared with an unpaired *t*-test analysis. Hypoxia and hypercapnia data were analysed using a general linear model to perform an analysis of variance (ANOVA). Significance was set at *p*<0.05 for all statistical tests.

Results

Subject characteristics and sex ratios are summarised in Table 1. Subjects were similar in age and height. By design, adults with MetSyn had significantly higher weight, BMI, waist circumference, blood pressure, and lower high density lipoprotein (HDL) than healthy controls (*p*<0.05). Insulin concentration was also greater in adults with MetSyn (*p*<0.05). Plasma triglyceride concentration tended to be higher in adults with MetSyn (*p*=0.08). Of the adults with MetSyn, eight met the criterion for waist circumference, one for plasma

glucose, six for HDL, three for triglycerides, and nine for blood pressure. None of the healthy adults met any of the criteria for MetSyn.

Systemic responses to hypoxia

Systemic haemodynamic values are summarised in Table 2. Heart rate increased at 80% S_pO_2 ($p < 0.05$) and did not differ between groups. MABP was greater in adults with MetSyn ($p < 0.05$) but did not change in either group with hypoxia. By design, S_pO_2 was reduced with hypoxia ($p < 0.05$) similarly between groups. P_{ETCO_2} was similar between groups and did not change with hypoxia, allowing us to specifically test hypoxic vasodilation. V_E increased at 80% S_pO_2 ($p < 0.05$), and did not differ between groups.

Cerebral responses to hypoxia

MCAv and CVCi values are presented in Table 2. MCAv values were similar between groups and condition but CVCi was lower in adults with MetSyn compared to healthy controls (main effect of group, $p < 0.05$, Table 2). There was also a main effect of hypoxia on CVCi ($p < 0.05$). Group mean CVCi- S_pO_2 relationships are illustrated in Figure 1(A). Absolute $\Delta CVCi$ (Figure 1(B)), relative $\Delta CVCi$ (% $\Delta CVCi$, data not shown) and hypoxia reactivity ($\Delta CVCi/\Delta S_pO_2\%$, Figure 1(C)) were all lower in adults with MetSyn (main effect of group, $p < 0.05$). There was a main effect of hypoxia intensity on both $\Delta CVCi$ (Figure 1(B), $p < 0.05$) and % $\Delta CVCi$ (data not shown). When data are expressed and analysed as $\Delta MCAv$, % $\Delta MCAv$, and $\Delta MCAv$ reactivity, conclusions remain the same as CVCi (data not shown). Analysing data as cerebrovascular resistance index (CVRi) absolute change, relative change, and reactivity also yields the same conclusions (data not shown).

Systemic responses to hypercapnia

Systemic haemodynamic values are summarised in Table 2. Heart rate did not differ between groups or between baseline and hypercapnia. MABP was greater in adults with MetSyn ($p < 0.05$), but did not change in either group with hypercapnia. Hypercapnia increased P_{ETCO_2} ($p < 0.05$) and S_pO_2 similarly ($p < 0.05$), but responses did not differ between groups. Due to data storage error, we were only able to analyse V_E for three adults with MetSyn and three healthy controls. Hypercapnia increased V_E ($p < 0.05$) but did not differ between groups.

Cerebral responses to hypercapnia

MCAv and CVCi values are presented in Table 2. MCAv values were similar between groups, but CVCi was lower in adults with MetSyn compared to healthy controls (main effect of group, $p < 0.05$, Table 2). There was a main effect of hypercapnia on both MCAv and CVCi ($p < 0.05$, Table 2). Group mean CVCi- P_{ETCO_2} relationships are illustrated in Figure 2(A). There was not a main effect of group on $\Delta CVCi$ (Figure 2(B)), % $\Delta CVCi$ (data not shown) or CVCi reactivity ($\Delta CVCi/\Delta mm\ Hg\ CO_2$, Figure 2(C)). Conclusions drawn from statistical comparisons are unaltered if data are expressed as $\Delta MCAv$, % $\Delta MCAv$ or as MCAv reactivity (data not shown). Further, conclusions are upheld when data are expressed as absolute change, relative change and reactivity of CVRi (data not shown).

Discussion

We hypothesised that adults with MetSyn would exhibit reduced cerebrovascular dilation to both hypoxia and hypercapnia. We studied younger adults, removing the confounding influence of primary aging and emphasizing the cumulative impact of MetSyn criteria before onset of clinically overt cerebrovascular disease. Using this approach, our data demonstrate that adults with MetSyn exhibited: (1) impaired cerebrovascular responses to

hypoxia and (2) preserved hypercapnia-induced cerebral vasodilation. These findings indicate that younger adults with MetSyn exhibit impaired cerebrovascular function prior to clinical presentation of metabolic or cardiovascular disease, and contribute novel physiologic insight into why adults with MetSyn are at greater risk of cerebrovascular disease and stroke.

Hypoxia

These data demonstrate that adults with MetSyn have blunted cerebral vasodilation to hypoxia whether data was expressed as absolute, relative, or stimulus-response ΔCVCi (Figure 1, main effect of group). Additionally conclusions remain the same if the data is expressed as MCAv or as CVRi . Hyperventilation-induced hypocapnia and concomitant vasoconstriction is a theoretical confounder of cerebrovascular responsiveness to hypoxia. We were careful to maintain P_{ETCO_2} at eupneic levels during exposure to hypoxia.

We postulate that either the threshold for hypoxic dilation is shifted in adults with MetSyn or these adults are closer to maximal hypoxia-mediated vasodilation at baseline, limiting dilator capacity. If their hypoxic dilation threshold is shifted, adults with MetSyn may maximally vasodilate at more severe levels of desaturation ($\text{S}_\text{p}\text{O}_2 < 80\%$). However, we did not test more severe levels of hypoxia for subject safety, and because 80% $\text{S}_\text{p}\text{O}_2$ encompasses many clinically relevant conditions (i.e. sleep disordered breathing). Dilator capacity would also be severely limited if these adults are close to their maximal hypoxic-mediated vasodilation at baseline. This may be a result of unfavourable inward vascular remodelling, which has been demonstrated in animal models of MetSyn.⁸ Regardless of aetiology, adults with MetSyn may be predisposed to cerebral ischaemia when exposed to hypoxic stressors. In turn, this may promote decrements in cognition¹⁴ or vascular function.¹⁵

Hypercapnia

Contrary to our hypothesis, adults with MetSyn demonstrated preserved hypercapnia reactivity regardless of data expression. The relatively young age of our subjects with MetSyn (37 ± 3 yrs) may indicate that they have not had MetSyn long enough for the multi-component disease to impart its full negative effects. Consistent with this concept, MetSyn has been established as an independent predictor of reduced cerebral vasomotor reactivity to CO_2 in older patients with atherosclerosis.⁹ However, if MetSyn progresses to type II diabetes, then the MetSyn criteria may no longer be as important for stroke risk as atherosclerotic vascular disease.¹⁶ Taken together, these data indicate that as MetSyn progresses to cardiovascular and metabolic disease in humans, hypercapnic reactivity may be lost. Along these lines, the age of our subjects might suggest that younger adults with MetSyn utilise redundant vasodilator signals to achieve normal hypercapnic dilation but it takes years of MetSyn to lose compensatory pathways.

A second explanation is that we may have underestimated or masked any difference in responsiveness to hypercapnia between the groups. We co-administered hyperoxia to prevent arterial oxygen desaturation, which may limit the increase in blood velocity and blood pressure.¹⁷ If hyperoxia prevented a greater increase of velocity in the healthy controls and a blood pressure increase in the adults with MetSyn, then hypercapnia performed under normoxia conditions may result in a significantly reduced ΔCVCi in the adults with MetSyn and alter our conclusions.

Potential vasodilator mechanisms

The mechanistic contributions to hypoxia- and hypercapnia-mediated vasodilation remain obscure as reviews have highlighted the influence of complementary or overlapping

mechanisms.¹⁸ Consistent with this concept, significant within-group response variability to hypoxia (Figure 1(C)) and hypercapnia (Figure 2(C)) indicates that, despite tight experimental control, there is not a uniform response to each stimulus within group. When taken in context with animal studies, there appear to be several testable hypotheses regarding potential pathogenic mechanisms of cerebrovascular impairment in MetSyn.

Hypoxia studies performed primarily in healthy humans and animals have provided mixed conclusions. Nitric oxide (NO) has been shown to be both obligatory^{19,20} and not required.^{21,22} Similarly, prostaglandins may^{22,23} or may not²⁴ be important. Even less is known about how MetSyn may affect hypoxic vasodilator mechanisms. Though isolated middle cerebral arteries from obese Zucker rats (OZR) have reduced hypoxic vasodilation,²⁵ studies demonstrate both a conservation²³ and an impairment²⁶ in endothelial NO formation depending on pharmacological stimulus and vessel studied. Reduced prostaglandin contribution²³ and potassium channel dysfunction^{26,27} in OZR have been more consistent findings.

Hypercapnia-mediated vasodilation in humans also remains inconclusive. Prostaglandins^{23,24,28,29} and vascular smooth muscle potassium channels^{26,27} each appear to contribute to vasodilation, while the contribution of NO has been shown to be both essential^{20,30} and non-obligatory.^{21,31} It is unclear how MetSyn may affect or alter signalling pathways in humans, but an important idea to test is that younger adults with MetSyn utilise redundant mechanisms to evoke preserved hypercapnic vasodilation.

Experimental considerations

Transcranial Doppler does not measure middle cerebral artery diameter and therefore cannot quantify cerebral blood flow. However, studies suggest that the diameter of the middle cerebral artery is not altered with physiological challenges^{32,33} meaning that changes in velocity reflect changes in cerebral blood flow with a reasonable degree of accuracy.³⁴

We propose that the cumulative effect of MetSyn criteria, rather than hypertension alone, is the key detriment negatively impacting cerebral vessel function. Hypertension is a key risk factor for stroke and may be a crucial influence on cerebrovascular dysfunction.³⁵ This is a matter of debate, however, as hypertension was not associated with decreased cerebral vasomotor reactivity to CO₂.⁹ To investigate the role of hypertension in impaired vascular regulation in our subjects, we correlated baseline blood pressure to hypoxia and hypercapnia reactivity values and found no relationship (data not shown). Therefore, the combined impact of the MetSyn criteria may prove more detrimental to cerebrovascular function than any individual criterion in subclinical disease.

The utilisation of finger pulse oximeter (S_pO₂) as our marker of hypoxia is not as strong as using arterial blood gas measurements. However, excellent agreement has been observed between S_pO₂ and arterial oxygen saturation spanning the range between 70–100%.³⁶ Also, we have no reason to believe the oxyhaemoglobin dissociation curve is altered in MetSyn adults. Therefore, we assume S_pO₂ is a valid measure of arterial oxygen saturation in both groups and we do not expect that it significantly impacts our results or interpretation.

We relied on self-report of sleep apnea. One subject with MetSyn reported having a continuous positive airway pressure (CPAP) machine, but had a normal desaturation event index without wearing it. This is important as the relationship between metabolic disorders and sleep-disordered breathing is multidirectional,³⁷ and sleep apnea has been shown to decrease cerebral vasomotor reactivity to hypoxia and hypercapnia.¹³ However, when the individual was excluded from data analysis our conclusions were unchanged so the subject was included in all analyses.

Clinical perspectives

Cerebral vasomotor reactivity reflects the ability of distal cerebral arteries to respond to a homeostatic perturbation³⁸ and is important in stabilising ventilation during sleep-disordered breathing.²⁹ Reduced hypoxia reactivity has been shown in adults with sleep-disordered breathing.¹³ Consistent with these ideas, MetSyn increases the risk of stroke threefold in men with sleep-disordered breathing.³⁹ This study adds to the current body of literature by suggesting a portion of the increased risk of sleep-disordered breathing in adults with MetSyn is due to impaired vasodilation to a clinically relevant level of hypoxaemia. Adults with MetSyn may experience more severe nightly ischaemic episodes, which could lead to higher susceptibility to chronic decrements in cognitive¹⁴ and vascular function.¹⁵ In turn, this may promote respiratory instability and sleep disordered breathing.

There is evidence suggesting an association between MetSyn and cognitive dysfunction,^{40,41} although the impact on cerebral vascular responsiveness was not assessed. Taken together with our data, impaired cerebral vasodilation is one potential link between MetSyn and poor cognitive outcomes.

It is known that MetSyn increases the risk of stroke twofold.³ The current study provides additional insight into cerebrovascular disease onset at a point where stroke or cerebrovascular disease may not manifest for decades, as the average age of stroke is approximately 68 years of age.⁴² Considering these stroke statistics, our novel findings open a 20–30 year treatment window for therapeutic interventions to prevent or reverse cerebrovascular disease in relatively younger adults with MetSyn.

Conclusion

These findings provide novel insight into the cerebrovascular function of adults with MetSyn who clearly demonstrate a failure to appropriately respond to reductions in cerebral oxygen delivery. The negative effects of MetSyn on cerebral vasculature appear specific to hypoxia in these relatively young adults. The results of this study provide researchers and clinicians with fundamental physiologic insight necessary to pursue interventions to improve cerebrovascular function in relatively young adults with MetSyn to reduce the risk and severity of cerebrovascular disease.

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Figure 1.

Isocapnic hypoxia. (A) Group mean CVCi – S_pO_2 values in metabolic syndrome (MetSyn) and healthy adults; (B) Group mean absolute $\Delta CVCi$ to 90% and 80% S_pO_2 ; (C) Individual subject and group mean stimulus-response slopes of CVCi at 90% and 80% S_pO_2 (a negative value reflects vasodilation).

$\Delta CVCi$: cerebral vasodilation; CVCi: cerebrovascular conductance index; S_pO_2 : arterial oxygen saturation. All group data are presented as group mean $\pm$ SE.

*Main effect of S_pO_2 80% hypoxia on CVCi v. baseline ($p < 0.05$).

†Main effect of group ($p < 0.05$).

‡Main effect of S_pO_2 80% hypoxia vs S_pO_2 90% ($p < 0.05$).

Figure 2.

Hyperoxic hypercapnia. (A) Group mean CVCi and PET_{CO2} values in metabolic syndrome (MetSyn) and healthy adults; (B) Absolute ΔCVCi group means ($p=0.66$); (C) Individual and group mean stimulus-response slopes ($p=0.71$, positive value reflects vasodilation). CVCi: cerebrovascular conductance index; PET_{CO2}: end tidal carbon dioxide.

All group data are presented as group mean $\pm$ SE.

*Main effect of hypercapnia on CVCi ($p<0.05$).

†Main effect of group ($p<0.05$).

Table 1

Subject characteristics.

	Healthy (n=10)	MetSyn (n=9)
Sex (M/F)	6/4	7/2
Age (years)	32±2	37±3
Height (m)	1.8±0.2	1.8±0.3
Weight (kg) *	73±3	121±11
BMI (kg/m ²) *	23±1	39±3
Waist (cm) *	84±3	120±6
Glucose (mmol/L)	4.4±0.1	5.1±0.4
Triglyceride (mmol/L)	0.8±0.1	1.5±0.3
HDL (mmol/L) *	1.7±0.1	1.0±0.1
Insulin (pmol/L) *	70±8	137±23
SBP (mm Hg) *	124±2	138±4
DBP (mm Hg) *	78±3	89±3
MABP (mm Hg) *	92±2	107±3

Data are presented as mean ± SE.

BMI: body mass index; DBP: diastolic blood pressure; HDL: high density lipoprotein; MABP: mean arterial blood pressure; MetSyn: metabolic syndrome; SBP: systolic blood pressure.

* Significantly different from healthy controls ($p<0.05$).

Table 2

Systemic and cerebral responses to hypoxia and hypercapnia.

	Hypoxia			Hypercapnia	
	Baseline	90% SpO₂	80% SpO₂	Baseline	+ 10 mm Hg P_{ET}CO₂
HR (beats/min) *					
Healthy	65±4	71±5	76±4	65±4	65±4
MetSyn	67±4	74±4	78±4	69±3	68±2
MABP (mm Hg) ‡					
Healthy	90±2	91±2	90±3	87±2	90±2
MetSyn	105±4	106±4	109±4	108±3	111±3
SpO₂ (%) *†					
Healthy	98±0	89±1	80±1	97±1	98±0
MetSyn	97±0	89±0	80±0	97±0	99±0
P_{ET}CO₂ (mm Hg) †					
Healthy	33±2	34±2	34±2	33±1	42±1
MetSyn	34±1	34±1	33±1	32±2	42±2
V_E (L/min) *†					
Healthy	11±1	13±1	18±3	9±1	12±0
MetSyn	10±0	13±2	15±2	9±0	15±2
MCAv (cm/s) *†					
Healthy	58±3	64±4	70±4	65±3	75±4
MetSyn	61±5	62±6	68±6	58±5	80±4
CVCi (cm/s/mm Hg) *†‡					
Healthy	64±3	71±4	78±5	64±4	84±5
MetSyn	61±5	62±5	68±5	55±5	73±5

CVCi: cerebrovascular conductance index; HR: heart rate; MABP: mean arterial blood pressure; MCAv: middle cerebral artery blood velocity; MetSyn: metabolic syndrome; P_{ET}CO₂: end tidal carbon dioxide; SpO₂: pulse oximeter arterial oxygen saturation; V_E: minute ventilation.

Data are presented as mean±SE.

* Main effect of hypoxia ($p<0.05$).

† Main effect of hypercapnia ($p<0.05$).

‡ Main effect of group ($p<0.05$).