

Transcutaneous Carbon Dioxide Treatment Is Capable of Reducing Peripheral Vascular Resistance in Hypertensive Patients

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Abstract. *Aim:* We aimed to investigate the effects of a single carbon dioxide (CO₂) treatment on arterial stiffness by monitoring the changes of aortic pulse-wave velocity (PWV) and aortic augmentation index (AIXao), which are indicators of arterial stiffness. *Patients and Methods:* PWV and AIXao were measured by an invasively validated oscillometric device. The measurements of stiffness parameters were performed before the CO₂ treatment, and at 1, 4 and 8 h after the first treatment. *Results:* Thirty-one patients were included. No significant changes were found in PWV. AIXao decreased significantly 1 h and 4 h after CO₂ treatment compared to baseline values ($p=0.034$ and $p<0.001$). AIXao increased 8 h after the CO₂ treatment, but remained significantly lower than baseline AIXao values ($p=0.016$). *Conclusion:* CO₂ treatment is capable of reducing peripheral vascular resistance. We hypothesize that CO₂ is not only a temporal vasodilator but is also capable of activating vasodilation pathways.

The transcutaneous administration of carbon dioxide (CO₂), further referred to as ‘CO₂ treatment’, has been used for curative purposes for decades. The first article investigating the medicinal use of CO₂ was published by Brandi *et al.* in 1932 (1). CO₂ passes freely through membranes and has a well-known vasodilation effect. Both *in vitro* and *in vivo* studies have demonstrated a rightward shift of the oxygen–hemoglobin dissociation curve after administration of CO₂.

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Sakai *et al.* described this as an “artificial Bohr-effect”. This was responsible for the increased partial pressure of oxygen and the decreased pH which were shown *in vivo* (2). The findings of Minamiyama and Yamamoto confirmed these effects by using intra-vital microscopy video imaging to demonstrate subcutaneous vasodilation after CO₂ administration. In addition, CO₂ was shown to increase the blood flow rate in the observed subcutaneous vessels (3). CO₂ treatment is used to cure several diseases such as peripheral arterial and venous disorders (*e.g.* claudication, and lower limb ulcer), heart diseases (*e.g.* hypertension, and heart failure) and immunological disorders (*e.g.* Raynaud’s syndrome) (4, 5). The pathophysiological link between these conditions is the presence of excessive oxidative stress.

The evidence of the relation between CO₂ treatment and oxidative stress is limited. However, Veselá and Wilhelm found CO₂ to play a protective role in scavenging free radicals and suppressing oxidative metabolism (6). A recent study demonstrated that CO₂ treatment is capable of reducing the level of asymmetric dimethylarginine, which is a marker of oxidative stress (7). Another study suggested that the transcutaneous application of CO₂ could have therapeutic effects on muscle atrophy (8). In short, CO₂ treatment is a non-invasive, highly effective, low-cost treatment capable of easing the symptoms of arterial and venous diseases possibly due vasodilatation and reduction of oxidative stress. However, there is no evidence of changes in vascular status after CO₂ treatment as far as we are aware.

Aortic pulse-wave velocity (PWV) and aortic augmentation index (AIXao) are widely used and recognized indicators of arterial stiffness (9, 11). Studies indicated that PWV is an independent predictor of primary coronary events (12) and fatal stroke (13) among hypertensive patients. AIXao is correlated with the degree of coronary artery disease (14), and predicts mortality in patients with end-stage renal failure (15). Moreover, according to Van Trijp *et al.*,

AIXao can be used as tool for estimation of coronary heart disease risk, especially among young adults (16).

The aim of this study was to investigate the effects of a single CO₂ treatment on arterial stiffness by monitoring the changes of PWV and AIXao.

Patients and Methods

Study design. The present study was performed at our ISO 9001-accredited Cardiology Rehabilitation Inpatient Unit from April 2017 to December 2017. Non-smoker, abstinent from alcohol, hypertensive patients were enrolled. Patients who had previously received CO₂ treatment were excluded. Moreover, patients who had suffered from myocardial infarction, stroke or undergone open surgery less than a year before the study were also excluded. Additionally, individuals diagnosed with any kind of cancer or kidney injury were also excluded. Informed written consent was obtained from every patient. This patient selection protocol was used in a previous study investigating the effects of CO₂ treatment on the nitric oxide system (7).

PWV and AIXao were measured by an invasively validated oscillometric device according to the manufacturer's protocol (Arteriograph; TensioMed Kft., Budapest, Hungary) (17). This programmable device is capable of measuring PWV and AIXao simultaneously using a special upper arm cuff which is fitted with a pressure sensor. All of the involved individuals were attending a 3-week-long cardiac rehabilitation.

Measurements were performed before the CO₂ treatment (baseline), and at 1 4 and 8 hours after the treatment. CO₂ gas was administered for 35 minutes in a plastic bag sealed at mid-thoracic level, as previously described by Fabry *et al.* (4). The measurements of stiffness parameters were performed in sitting position from 8 a.m. to 18 p.m. The patients did not receive any medication besides their regular antihypertensive drugs during the measurements.

The study protocol was approved by the Regional Ethics Committee of University of Pécs, Pécs, Hungary (Permission No. 5919), in accordance with the 2008 Helsinki declaration.

Statistical analysis. Statistical analysis was performed by IBM SPSS Statistics for Windows Version 22 (IBM Corp., New York, NY, USA). According to Shapiro–Wilk test, PWV and AIXao samples were normally distributed and, thus, were used to demonstrate results (95% confidence interval for mean). Differences during the follow-up were investigated by paired-sample *t*-test. Independent sample *t*-test was used to compare the stiffness parameters between diabetic patients and non-diabetic patients. Pearson's correlation test was used to reveal correlations. All *p*-values less than 0.05 were considered statistically significant.

Results

Initially, 35 patients were enrolled. Two patients were excluded because they did not tolerate the upper arm cuff for 8 hours. Due to technical reasons, only baseline values were recorded in the case of two patients; thus they were also excluded. Finally, the stiffness parameters of 31 patients were measured (18 male and 13 female; mean age=66.7±9.4 years).

Table I. Clinical characteristics of the study participants (n=31).

Characteristic	Value
Mean±SD age, years	66.7±9.4
Male, n (%)	18 (58)
Mean BMI±SD, kg/m ²	28.5±4.7
Diabetes type 2, n (%)	11 (35)
MI, n (%)	4 (13)
CABG, n (%)	9 (29)
EF, (%)	56.4±7.3
Mean WBC count±SD, ×10 ⁹ /l	5.97±1.77

BMI: Body mass index; MI: myocardial infarction; CABG: coronary artery bypass surgery; EF: ejection fraction; WBC: white blood cell count.

Table II. Detailed results of the monitored parameters of the study participants (n=31).

	Baseline	1h	4h	8h
AIXao±SD, (%)	35.82±11.67	31.41±8.91	27.79±9.37	30.9±8.04
PVW±SD, (m/s)	9.52±2.12	8.91±2.43	8.89±2.01	9.39±2.66
SBP±SD, (mmHg)	125±12	123±14	119±7	119±8
DBP±SD, (mmHg)	72±8	70±11	68±7	67±6

AIXao: Aortic augmentation index; PVW: aortic pulse wave velocity; SBP: systolic blood pressure; DBP diastolic blood pressure.

Clinical characteristics of the participants are shown in Table I.

Regarding the PWV, no significant changes were found when comparing the baseline PWV to values at 1 hour (*p*=0.097), 4 hours (*p*=0.055) or 8 hours (*p*=0.785) after CO₂ treatment. Changes of the PWV after CO₂ treatment are shown in Figure 1.

AIXao decreased significantly 1 hour after the CO₂ treatment compared to the baseline values (*p*=0.034). Four hours after the treatment, AIXao decreased further and remained significantly lower compared to baseline (*p*<0.001). Finally, AIXao started to increase 8 hours after the CO₂ treatment but still remained significantly lower than baseline values (*p*=0.016). Changes of AIXao after CO₂ treatment are shown in Figure 2.

No significant differences were found between baseline AIXao and AIXao measured 1, 4 and 8 hours after treatment among patients suffering from diabetes mellitus (*p*=0.955, *p*=0.077 and *p*=0.581, respectively).

Detailed results of the monitored parameters are shown in Table II.

None of the baseline medications (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-receptor blockers, statins, diuretics, antidiabetics, antiplatelet treatment, proton pump inhibitors, H₂-receptor blockers) showed no effect on stiffness parameters.

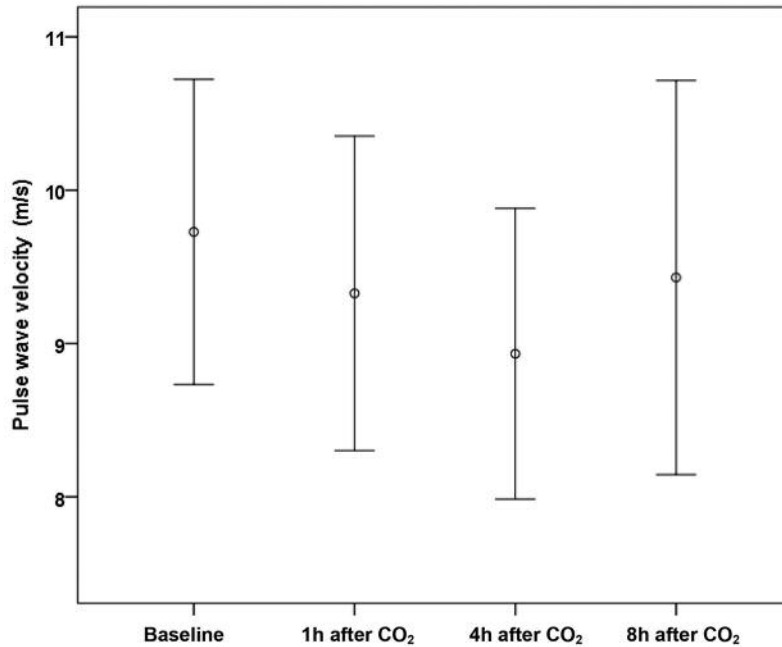


Figure 1. Pulse wave velocity before and after CO₂ treatment.

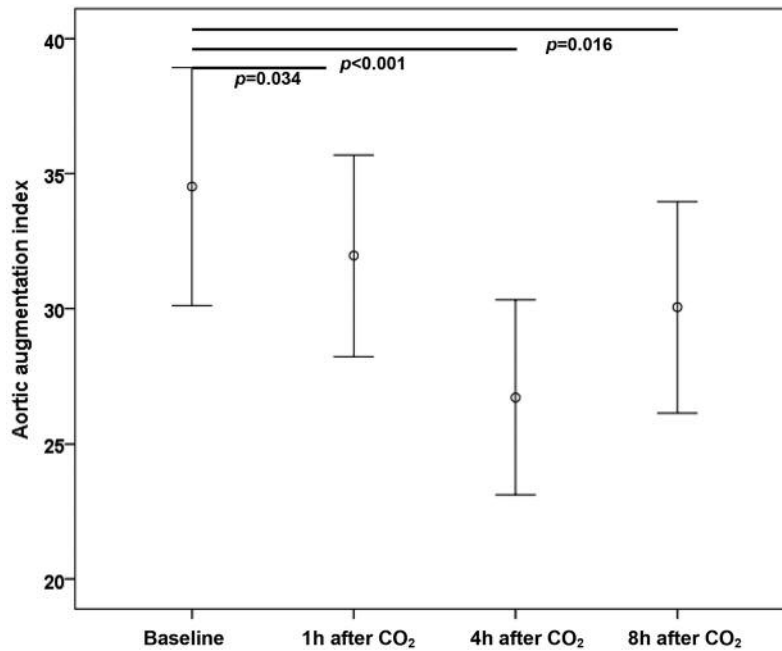


Figure 2. Aortic augmentation index after CO₂ treatment.

Discussion

To the best of our knowledge, this is the first study investigating the changes of arterial stiffness (PWV and AIXao) parameters after a single CO₂ treatment.

Aortic stiffness develops because the elastic fibers of the aorta are replaced by collagen fibers (18). This histopathological change is represented by the speed of the PWV. The stiffening of the aorta is a slow procedure; significant changes require years. Taking this into account,

it is not surprising that a single CO₂ treatment did not significantly change the PWV. On the other hand, AIXao represents the tone of small arterioles. Accordingly, the changes of the AIXao can be regarded as changes of peripheral vascular resistance (15, 19). The main result of this study is that even a single 35-minute-long CO₂ treatment is capable of reducing AIXao significantly. AIXao decreased almost instantly after the CO₂ treatment. However, AIXao started to increase 8 hours after the CO₂ treatment but still remained significantly lower than the baseline AIXao value. This relatively quick change of peripheral resistance can be explained by the physical properties of CO₂. Interestingly, the most pronounced effect of CO₂ treatment on the peripheral resistance developed 4 hours after the treatment. This indicates that transcutaneously applied CO₂ is not only a temporal vasodilator but it is capable of activating endogenous pathways leading to vasodilatation. The results of our previous study partly confirmed this hypothesis. Our study showed that CO₂ treatment has beneficial effects on the NO pathway (7). NO-related vasodilatation may be an explanation for the delayed response of AIXao.

In line with the study of Zhang *et al.*, no differences were found when comparing the stiffness parameters of diabetic patients with those of the non-diabetic patients (20). Another interesting result of this study is that the above-mentioned changes of AIXao were not demonstrable in patients suffering from diabetes mellitus. The vascular system of diabetic patients seems to be less responsive to the beneficial effects of CO₂ treatment; this is most likely due to the well-known micro- and macrovascular complications of diabetes (21).

According to previous studies, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and statins have been shown to improve PWV and AIXao values (22-25). These beneficial effects were not demonstrable in our patients, probably due to the small sample size.

Study limitations. The lack of a control group can be addressed as a limitation. However, the aim of this study was only to demonstrate the effects of a single CO₂ treatment on stiffness parameters. Moreover, the effectiveness of CO₂ treatment has been proven by other studies (1-5, 7).

Conclusion

Our study suggests that even a single CO₂ treatment is capable of reducing peripheral vascular resistance. Furthermore, because of the 4-hour delay in AIXao change observed here, we hypothesize that CO₂ is not only a temporal vasodilator but is also capable of activating endogenous pathways leading to vasodilatation. However, further larger studies are necessary to confirm our hypothesis and to describe the beneficial effects of CO₂ treatment.

Conflicts of Interest

The Authors declare that there is no conflict of interests regarding the publication of this article.

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