

Effects of Carbon Dioxide Angiography on Endothelial Functions in Lower Extremity Arteries via Flow Mediated Vasodilatation

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ABSTRACT

Introduction: Carbon dioxide angiography is widely used specifically in screening peripheral venous system, lower extremity arteries, visceral arteries and abdominal aorta in patients with renal insufficiency and hypersensitivity to contrast agents. Efficacy and safety was revealed but effects on endothelial functions have not been documented. We aimed to document the effects of carbon dioxide angiography on endothelial functions in lower extremity arteries via noninvasively with flow mediated vasodilatation.

Materials and Methods: Sixteen patients with lower extremity arteriosclerosis and renal insufficiency were included. All patients were evaluated with CO₂ angiography for peripheral arteriosclerosis. Lower extremity endothelial functions were evaluated noninvasively with flow-mediated vasodilatation from popliteal artery before, immediately after and one hour after CO₂ angiography. The vessel diameter, flow rate and dilatation percentage were calculated and all result were compared.

Results: The vessel diameter, flow rate and dilatation percentage were similar at baseline and one hour after angiography. The measurements immediately after angiography were decreased compared to baseline ($p < 0.001$). The measurements returned to baseline after one hour.

Conclusion: Despite safety of CO₂ angiography in screening vasculature, side effects like embolism, gas trapping, and hypersensitivity were documented Our study revealed that it has temporary negative effects on endothelial functions immediately after procedure proved by objective parameters. However, the clinical exact side effects and interactions should be further studied.

Keywords: Carbon dioxide angiography; Endothelial dysfunction; Flow mediated vasodilatation; Peripheral vascular disease

Abbreviations: FMD: Flow Mediated Vasodilatation; SPSS: Statistical Package for the Social Sciences

INTRODUCTION

Carbon dioxide was used in medical screening as early as 1920s as contrast media and in vascular imaging in 1980s. Recently CO₂ is revealed to be an effective and safe angiographic contrast agent in the periphery arterial and venous circulation [1]. However, its use is limited in patients with renal failure and hypersensitivity due to arrhythmic and neurotoxic effects in cerebral and cardiac circulation [2,3].

Carbon dioxide has higher solubility, lower viscosity and fewer side effects than actual contrast agents, but air contamination [4], coronary and cerebral embolism, image degradation, incomplete filling of the large vessels and sometimes need for classical contrast

agents are main drawbacks [5,6].

Endothelial vasoactive response is a marker for endothelial dysfunction and may affect endothelial cell metabolism [7]. It is possible to measure endothelial functions by pharmacologically or mechanically inducing vasodilatation. Pharmacologic method is easy and non-invasive [8,9]. Flow mediated vasodilatation (FMD) is used to evaluate vascular vasomotion in systemic arteries with an ultrasound. Vascular response to nitrate and vascular ischemia via a percentage change in arterial diameter from the baseline is evaluated [10-12].

We hypothesized that CO₂ angiography affects endothelial functions either positively or negatively. For that purpose we

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measured flow mediated vasodilatation in lower extremity arteries following CO₂ angiography.

MATERIALS AND METHODS

The study was approved by institutional ethical Committee waiving individual consent due to its retrospective nature. Patients with renal insufficiency admitted to our hospital for evaluation of peripheral arterial disease between July 2016 and August 2019. Doppler ultrasonography was performed by same experienced operator at initial examination and ones with total occlusion were excluded. Sixteen patients underwent diagnostic CO₂ angiography by same operator. Antegrade femoral artery approach guided by doppler ultrasonography *via* seldinger method with proper catheters was used. Carbon dioxide was administrated at 10 to 20 ml/sec for 1.5 seconds and diagnostic images were obtained. Endothelial functions were determined before, immediately after and 1 hour after CO₂ angiography by flow-mediated vasodilatation. All measurements were made three times and means of measurements took in consideration for statistical calculations. Bilateral popliteal artery FMD at baseline was measured by a 9 MHz linear array transducer, placed over the popliteal artery just distal to the popliteal fossa. Simultaneous diameter and velocity signals were obtained in duplex mode at a pulsed frequency of 5 MHz and corrected with an angle of 60°. The blood pressure cuff was applied on the leg and inflated to 300 mm Hg for 4.5 min for ischemia. It was deflated shortly after. After 1 minute and at 1 hour, the ultrasound scan of popliteal artery was obtained, which shows the endothelial-dependent dilation due to shear-induced endothelial nitric oxide production [13,14]. The percent diameter change for FMD and other parameters of vasomotion were calculated in relation to its respective scans. Then all measurements were compared.

STATISTICAL ANALYSIS

The statistical package SPSS (Statistical Package for the Social Sciences, version 17.0, SSPS Inc, Chicago, Ill, USA) was used for statistical analysis. Continuous variables were expressed as means \pm standard deviation. Categorical variables were expressed as the total number (percentage). Analysis was performed using Student *t*-test. Categorical data were compared against a chi-squared distribution. A *p* value <0.05 was set as significant.

RESULTS

There were 16 patients with renal insufficiency included in the study; 9 male and 7 female. The mean age of the patients was 73.56 \pm 6.05. All patients had a glomerular filtration rate <50 ml/min (19.20 \pm 8.72). Thirteen patients (81.2%) had diabetes, all had dyslipidemia, 12 (75%) had coronary artery disease and 12 (75%) had carotid stenosis >50%.

Baseline mean arterial diameter (mm), blood flow (ml), increase in blood flow (ml) and FMD (%) were 3.48 \pm 0.61 mm, 203.12

\pm 15.85 ml, 319.12 \pm 22.93 ml and 6.06 \pm 0.72% respectively. The baseline diameter, arterial blood flow, increase in blood flow and FMD decreased significantly immediately after angiography (*p*<0.001 for each), but returned to baseline levels one hour after Table 1. Baseline values and 1 hour after values were similar (*p*: 1.000).

DISCUSSION

For diagnostic purposes, intravascular liquid contrast agents were first used in 1924. There is ample evidence that iodinated contrast agents cause endothelial dysfunction, myocardial cell damage and coronary spasms. Moreover, iodinated contrast media can cause acute kidney injury [15]. The endothelial dysfunction is the consequence of a direct cytotoxic effect on renal tubular epithelial and endothelial cells. The reasons of the endothelial toxicity of contrast agents are the result of both direct proapoptotic effects and morphological derangements and induction of inflammation, oxidative stress and thrombosis [16]. Also shear stress stimulates endothelium to produce nitric oxide [17,18].

To overcome these complications CO₂ was used by needle injection in 1956, followed by catheter delivery [1,2]. It has higher solubility, lower viscosity and lower toxicity than actual contrast agents, but still has some shortcomings as gas trap in hallow space and embolism.

The relationship between CO₂ and endothelial dysfunction has not been revealed. In this study we observed short-term endothelial dysfunction documented by means of FMD measured non-invasively. Measurements returned to baseline 1 hour after angiography. The reason for temporary endothelial dysfunction is unclear. When we explore this relation, we observed that there are similarities between endothelial dysfunction occurring during decompression illness. This similarity was the rationale for conducting this study. However, the gas responsible for dysfunction is different [17,18]. It was reported previously that exposure of endothelial cells with air bubbles caused an influx of calcium through a stretch-activated channel, such as a transient receptor potential vanilloid family member, triggering the release of calcium from intracellular stores in decompression illness [18]. This gas contact with endothelium can promote released micro particles that reduced cell viability, increased apoptosis, and production of pro-inflammatory cytokines [15,17,18].

Endothelial dysfunction in popliteal artery has been studied in minor reports, but like mentioned above; these reports do not discuss angiographic results. It has been long mentioned that immobility and bending of legs can cause endothelial dysfunction, which was also demonstrated with FMD [19]. The endothelial dysfunction in popliteal artery was studied in patients with coronary artery disease, and it is concluded that first sign is disturbed FMD in popliteal artery [20]. Moreover, popliteal artery FMD was significantly decreases with aging [21]. Daily physical activity can

Table 1: Popliteal arterial data of flow mediated vasodilatation (endothelial-dependent dilation).

	t ₀	t ₁	t ₂	p ₁	p ₂
d (mm)	3.48 \pm 0.61	2.83 \pm 0.68	3.48 \pm 0.62	0.007	1.000
BF (ml/min)	203.12 \pm 15.85	169.25 \pm 28.18	203.12 \pm 15.96	<0.001	1.000
↑ in peak BF (%)	319.12 \pm 22.93	177.06 \pm 25.70	319.68 \pm 23.56	<0.001	1.000
Flow-mediated dilatation (%)	6.06 \pm 0.72	3.50 \pm 1.18	6.04 \pm 0.70	<0.001	1.000

t₀: baseline; t₁: immediately after angiography; t₂: 1 hour after angiography; diameter; p₁: t₀ vs. t₁; p₂: t₀ vs. t₂; BF: Blood Flow

improve popliteal artery FMD [22] therefore workplace strategies are suggested to prevent immobility induced endothelial dysfunction [23].

CONCLUSION

In conclusion, our study showed that CO₂ may cause temporary endothelial dysfunction in lower extremity arteries, but clinical significance is not known.

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