

## Case Report

# Arterial Thrombosis after Nitrous Oxide Recreative Abuse: A Case Report

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## ABSTRACT



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Nitrous oxide, also known as “laughing gas”, has been used for more than 150 years in medical practice, autonomously or in combination with other inhalation anesthetics, for pain relief, in various surgical interventions. In modern medicine, its use has

declined, due to its side effects and also because of the advent of newer, shorter-acting agents and newer inhaled anesthetics.

During the last few years, an increased recreational use of nitrous oxide was noted, mainly among the young people, because it is cheap and easily available. Until very recently, there wasn't much information about the toxicity of inhaled nitrous oxide, but now there are available data in the literature describing its serious consequences, which can permanently compromise the quality of life. We present the case of a 37-year-old woman, who was admitted into the Vascular Surgery

Clinic with signs of thrombosis of the left femoral artery, with a history of regular recreative use of nitrous oxide in the recent months.

**Keywords:** Arterial Thrombosis, Recreative Use, Nitrous Oxide, Homocysteine.

## INTRODUCTION

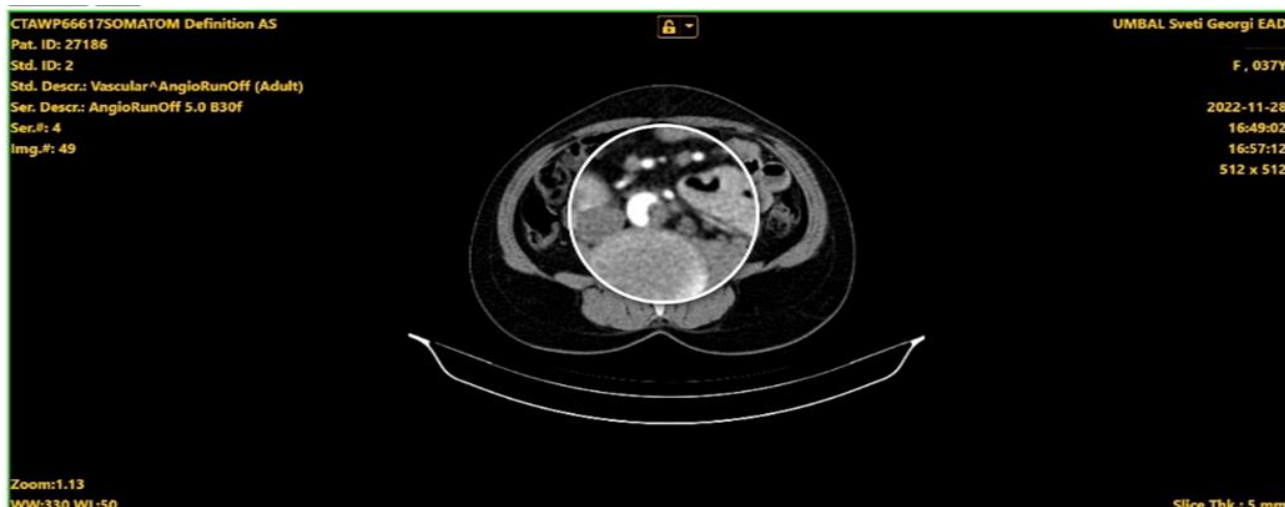
Nitrous oxide when inhaled recreationally can have significant effects, mostly on cognitive function such as euphoria, hallucinations and numbness of the extremities. These changes, along with its easy availability and the conviction among the younger generation that it is absolutely harmless to use, made laughing gas extremely popular. In addition to the side effects already known (diffusion into a closed air spaces, inactivation of the methionine synthase, diffusion hypoxia), in recent years, cases of deep venous thrombosis, pulmonary embolism and arterial thrombosis have been documented after nitrous oxide recreative use<sup>1,2</sup>. This case report aims to show the possible relationship between the nitrous oxide recreative use and the increased risk of cardiovascular events.

## CASE REPORT

A 37-year old female patient with no previous medical history of chronic diseases or systematic use of any medications, was admitted in the Emergency Department of our hospital with significant pain in the left leg causing impossible movement of the latter, without any neurologic symptoms. The use of Echo-Doppler found absence of pulsations in the left femoral, popliteal and distal tibial artery. Laboratory testing revealed increased

levels of serum fibrinogen (7.07 g/l, with reference level 4.5 g/l) and D-dimers (1.29 mg/l, reference level 0.5 mg/l), and with no other deviations of the other measured parameters. The patient reported that she used recreationally nitrous oxide regularly throughout the past few months. The patient had a history of a physiological childbirth and two voluntary abortions.

Thromboendarterectomy of the left iliac and left femoral artery was performed under spinal anesthesia. An hour after surgery, due to the recurrence of thrombosis which caused continuing ischemia, a new redo-thrombectomy surgery was performed. With a still insufficient clinical result of restored perfusion, the posterior plantar artery was also revised. Ultimately, normal revascularization was provided along with reversal of the heavy ischemia. CT angiography was performed postoperatively and showed an endovascular narrowing of the abdominal aorta, above its bifurcation up to 37 % of the vessel, on account of an asymmetric densely fused to the wall lesion, with unclear structure for a plaque or thrombus and the remaining segments of the abdominal aorta and arteries of the small pelvis and lower extremities were with normal presentation (Fig. 1 and 2).



**Figure 1.** CT-scan data of a thrombotic plaque above the aorta bifurcation, cross section.



**Figure 2.** CT-scan data of a thrombotic plaque above the aorta bifurcation, longitudinal section.

After surgery, patient received subcutaneously low molecular weight heparin (enoxaparin 6000 anti-XA IU/twice daily) and Clopidogrel 75 mg/daily. During hospital stay, patient was consulted by a cardiologist twice, troponin levels were measured (negative) and echocardiography was performed, which showed preserved dimensions of the heart chambers, intact valve apparatus and preserved ejection

fraction. A PCR test was performed for SARS-CoV-2 (negative) and also a roentgenography of the chest, which ruled out an active pulmonary disease. On the 3<sup>rd</sup> postoperative day, the levels of vitamin B12 (144 pmol/L, with reference level 145.4 pmol/L) and of homocysteine (73.5  $\mu$ mol/L, with reference level 12  $\mu$ mol/L) were tested. On the second postoperative day, the limb pain totally

faded away, patient was mobilized and was discharged from the hospital in improved general condition five days after surgery.

## DISCUSSION

The incidence of peripheral arterial thrombosis is 1,5 per 10000 patients, but the incidence of thrombus formation in arteries with high blood flow is extremely rare<sup>3</sup>. Upon patient's admission into the Vascular Surgery Clinic, we did not succeed in finding the cause of the thrombus formation. We did not test the mutation of heterozygous factor II, because it is associated with greater frequency of venous thrombosis compared to arterial one<sup>1</sup>. The patient denied any use of medication that could have caused this condition. Due to the history of nitrous oxide recreative use, we decided to test the levels of vitamin B12 and homocysteine<sup>4,5</sup>. The nitrous oxide reduces the levels of vitamin B12, which is a co-factor in the remethylation of homocysteine in the folate and methionine cycle. Impaired methionine metabolism leads to an increase in homocysteine levels in the blood, which in turn leads to a higher risk of thrombus formation and cardiovascular events. The mechanism of homocysteine's damaging action is not fully understood, but it is thought to decrease nitric oxide production, increase platelet aggregation, and enhance LDL oxidation with its vascular deposition<sup>4,5,6</sup>. Although the patient's vitamin B12 levels were not significantly decreased, homo-

cysteine levels were increased by 6-fold. Clinical studies have shown that symptoms of vitamin B12 deficiency can be observed in some patients with normal laboratory reference. This is also one of the reasons for the divergence of reference limits in different countries. For comparison, in Bulgaria these limits are 145.4 - 569 pmol/L, and in Japan 500 - 1300 pmol/L<sup>7</sup>. Therefore, it is accepted that in case of suspected vitamin B12 deficiency, homocysteine should also be tested<sup>8,9,10</sup>.

Arterial thrombosis has been associated with Covid-19 infection, but our patient had a negative PCR test, the chest X-ray did not show any active pulmonary disease, and there were no clinical or laboratory data on an inflammatory process. Genetic defect in methylenetetrahydrofolate reductase was not investigated because homocysteine levels did not increase by 40-fold or more and also because any vascular event did not occur before the age of 30<sup>5</sup>. Congenital clotting factors were also not investigated due to patient's denial to consent and due to the fact that she had no prior history of arterial thrombosis. However, considering the close relationship between nitrous oxide use and elevated homocysteine levels, we believe nitrous oxide use had at least partly contributed to the formation of arterial thrombosis in our patient. After discharge, patient was strongly advised to undergo genetic screening for congenital clotting factors and to retest homocysteine and vitamin

B12 levels at the next follow-up examination, as it is well known that early detection of inherited risk factors, predisposing to the development of thrombosis or embolism and initiation of adequate treatment could reduce the risk of reoccurrence of a vascular event.

## CONCLUSION

Our case shows that recreational use of nitrous oxide can lead to increased risk of thromboembolic complications even in previously healthy patients<sup>2</sup>. However, appropriately designed future studies are needed to confirm the relation of regular and heavy recreational use of nitrous oxide with thrombus formation and to raise public consciousness of the potential negative effects of nitrous oxide recreational use on young individuals.

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