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Case Report

Reduction of Coronary Artery Stenosis Following Oxyhydrogen and Gasotransmitter Nanobubble Infusions: A Case Report

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Abstract

Background: Evidence regarding intravenous therapeutic-gas nanobubbles incorporating hydrogen (H₂), oxygen (O₂), nitric oxide (NO), and other gasotransmitters in coronary artery disease (CAD) remains limited. Although conventional pharmacological and revascularization treatments improve outcomes, substantial regression of established coronary plaque remains difficult. **Methods:** Clinical records, examination findings, laboratory results, treatment documentation, imaging reports, and patient-reported outcomes were retrospectively reviewed. **Case Presentation:** A 68-year-old man with mild exertional angina and dyspnea had September 2023 coronary CT angiography showing 40–60% soft-plaque stenosis in the mid-left anterior descending artery (LAD) and less than 25% stenosis in the proximal and distal LAD and dominant right coronary artery (RCA). From March to August 2025, he received 73 intravenous infusions containing oxyhydrogen, nitric oxide, other gasotransmitters, and methylene blue, alongside atorvastatin and lifestyle counseling. Follow-up imaging on 7 August 2025 showed mid-LAD stenosis of 20–30% and mid-RCA stenosis of 10–20%. The patient reported symptom resolution and improved functional capacity. **Conclusions:** This case documents a temporal association between adjunctive nanobubble-based therapy, symptomatic improvement, and lower estimated stenosis on serial coronary imaging. Causality cannot be established from a single uncontrolled observation, and controlled studies with standardized imaging and safety assessment are required.

Keywords: coronary artery disease; nanobubbles; oxyhydrogen; gasotransmitters; methylene blue; coronary CT angiography; case report

1. Introduction

Atherosclerotic cardiovascular diseases—such as coronary artery disease (CAD), ischemic heart disease, and stroke—continue to be the leading cause of death worldwide [1]. In 2019, ischemic heart disease alone was responsible for around 9.14 million deaths, with a significant impact especially in low- and middle-income countries [1]. Despite notable progress in prevention and medical treatment, global mortality from cardiovascular disease (CVD) is expected to remain high, largely because of aging populations, with atherosclerosis playing a key role in sustaining this persistent burden [2].

Current medical treatments—particularly statins and other lipid-lowering drugs—have been proven to reduce cardiovascular events and can slow down or slightly reverse the buildup of atheroma [3]. Large imaging studies and meta-analyses using intravascular ultrasound and other techniques demonstrate that intensive lowering of LDL cholesterol leads to measurable reductions in plaque volume [3]. However, the degree of anatomical regression is generally modest and varies among patients. Consequently, statin therapy more commonly stabilizes plaques rather than consistently achieving substantial removal of existing soft atheroma in all patients [3].

Revascularization methods also have important drawbacks [4,5]. Percutaneous coronary intervention (PCI) with stenting can relieve specific areas of reduced blood flow and ease symptoms,

but it primarily treats focal flow-limiting lesions rather than the widespread atherosclerotic disease affecting the arterial system [4]. PCI can also lead to problems such as in-stent restenosis or the need for another revascularization procedure [5]. Long-term results depend on the type of blockage and the patient's other health conditions [4,5].

Coronary artery bypass grafting (CABG) provides durable revascularization for selected patients with multivessel or left main coronary artery disease but is an invasive procedure associated with graft failure—especially in saphenous vein grafts, which may deteriorate over time [4,6,7]. Additionally, perioperative complication and mortality risks may limit its use in certain patients [4]. Furthermore, neither CABG nor PCI directly targets the underlying systemic inflammation and metabolic factors that contribute to plaque development and instability [3,4].

Nanobubbles (NBs) are extremely small gas-filled particles, generally measuring less than 1 μm and commonly ranging from tens to hundreds of nanometers in diameter [8,9]. Their small size, low buoyancy, relative stability, and gas-carrying capacity have prompted investigation into their use as carriers for therapeutic gases and other agents [8,9]. NBs have been widely researched for targeted delivery systems, as their size and surface properties may enable controlled drug delivery and ultrasound-triggered release while potentially reducing systemic exposure [8,10]. Bioactive gases such as oxygen (O_2), hydrogen (H_2), nitric oxide (NO), and hydrogen sulfide (H_2S) have been investigated for their roles in oxygenation, redox regulation, inflammatory signaling, and vascular tone [10,11]. Incorporating these gases into microbubble or nanobubble platforms has been investigated as a strategy for improving gas delivery; however, evidence for targeted delivery to atherosclerotic plaques and clinical effects in CAD remains limited [9,10].

Methylene blue (MB) also has biological actions potentially relevant to vascular and mitochondrial function, including inhibition of soluble guanylate cyclase and nitric oxide synthase and activity as an alternative electron carrier in the mitochondrial respiratory chain [12,13]. Experimental studies suggest effects on oxidative stress and ischemia–reperfusion injury; however, cardiac responses may depend on the timing of administration, with both cardioprotective and cardiotoxic effects reported [12].

This case report describes a patient with CAD who experienced an apparent reduction in estimated left anterior descending (LAD) artery stenosis from 40–60% to 20–30% after undergoing comprehensive intravenous nanobubble therapy. The treatment involved a combination of hydrogen (H_2), oxygen (O_2), nitric oxide (NO), methylene blue (MB), and other gasotransmitters, with the proposed aims of enhancing microvascular blood flow, lowering oxidative stress, and supporting endothelial function [9–11]. This case documents a temporal association between nanobubble-based gasotransmitter therapy, symptomatic improvement, and lower estimated coronary stenosis and may support further investigation of this approach as an adjunctive therapy for CAD.

2. Case Presentation

2.1. Patient Information

A 68-year-old Asian man had hypothyroidism following total thyroidectomy for thyroid carcinoma eight years earlier and had received long-term thyroid hormone replacement therapy since surgery. His baseline medications and supplements were:

- Levothyroxine 175 mcg once daily
- Tadalafil 5 mg every two days
- Atorvastatin 10 mg once daily
- Vitamin D3 1,000 IU once each morning
- Krill oil supplement once daily
- ProArgi-9+ supplement twice daily
- Three 6 Types supplement once daily

He reported a moderately active lifestyle that included daily walking but limited structured exercise. He described a relatively balanced diet with moderate carbohydrate and fat intake and denied current smoking or significant alcohol consumption.

The patient reported mild exertional angina and dyspnea, particularly when climbing stairs or walking briskly for more than 30 minutes. There was no history of rest angina, syncope, or recent hospitalization for acute coronary syndrome.

2.2. Clinical Findings

At the initial evaluation on 22 March 2025, the recorded findings were:

- Blood pressure: 120/80 mmHg
- Heart rate: 86 beats/min, regular
- Peripheral oxygen saturation: 96% on room air
- Perfusion index: 7.7
- Cardiac auscultation: normal S1 and S2; no murmurs, rubs, or gallops
- Pulmonary auscultation: clear bilateral breath sounds; no wheezes, rales, or rhonchi
- New York Heart Association (NYHA) functional class I–II (no limitation of physical activity at rest, mild dyspnea only with moderate exertion)
- Canadian Cardiovascular Society (CCS) angina class II (angina occurring with moderate exertion such as brisk walking or climbing stairs, relieved by rest)

2.3. Timeline

Table 1. Timeline of diagnosis, intervention, and follow-up.

Date	Event	Findings or intervention
September 2023	Initial CAD detection	Coronary CT angiography revealed LAD mid-segment atherosclerosis (soft plaque) with 40–60% stenosis, proximal and distal LAD <25%, RCA dominant mid-segment <25%.
22 March 2025	Start of therapy	Began intravenous nanobubble infusion therapy consisting of oxyhydrogen (HHO), nitric oxide (NO), gasotransmitters, and methylene blue.
March–August 2025	Treatment course	Seventy-three sessions were completed over approximately 20 weeks. The patient reported progressive improvement in exercise tolerance and exertional symptoms.
6 August 2025	Laboratory follow-up	Lipid, inflammatory, cardiac, glycemic, and renal laboratory markers were assessed.
7 August 2025	Follow-up imaging	Coronary imaging described mid-LAD stenosis of 20–30% and dominant mid-RCA stenosis of 10–20%.

2.4. Diagnostic Assessment

Baseline coronary CT angiography in September 2023 reported a calcium score of 0, a normal left main coronary artery, mid-LAD soft plaque with mild-to-moderate stenosis of 40–60%, minimal

(<25%) stenosis of the proximal and distal LAD, a normal left circumflex artery, and a dominant RCA with mid-segment soft plaque and minimal (<25%) stenosis.

The available lipid and apolipoprotein measurements are summarized in Table 2.

Table 2. Lipid and apolipoprotein measurements before and after the infusion period.

Parameter	26 November 2024	6 August 2025	Reference range
Total cholesterol	167 mg/dL	165 mg/dL	—
HDL cholesterol	100 mg/dL	99 mg/dL	—
LDL cholesterol	55 mg/dL	55 mg/dL	—
Total cholesterol/HDL ratio	1.7	1.7	—
Triglycerides	62 mg/dL	58 mg/dL	—
Apolipoprotein A1	—	2.16 g/L*	1.04–2.02 g/L
Apolipoprotein B	—	0.44 g/L*	0.66–1.33 g/L
Apolipoprotein B/A1 ratio	—	0.20*	0.22–0.80
Lipoprotein(a)	—	<7.0 mg/dL	<75.0 mg/dL

*Value outside the stated laboratory reference range. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Laboratory testing on 6 August 2025 showed high-sensitivity C-reactive protein (hs-CRP) of 1.70 mg/L, high-sensitivity troponin (hs-Troponin) of 9.8 ng/L, creatine kinase (CK) of 199 U/L, creatine kinase-MB (CK-MB) of 3.90 ng/mL, and glycated hemoglobin (HbA1c) of 5.6%. The estimated glomerular filtration rate (eGFR) increased from 89 mL/min/1.73 m² on 26 November 2024 to 93 mL/min/1.73 m² on 6 August 2025.

No alternative diagnosis was documented; the coronary findings were considered consistent with atherosclerotic CAD. Follow-up coronary imaging on 7 August 2025 described a normal left main artery, mid-LAD stenosis of 20–30%, a normal left circumflex artery, and dominant mid-RCA stenosis of 10–20%.

2.5. Therapeutic Intervention

The patient underwent a comprehensive nanobubble infusion protocol consisting of hydrogen, oxygen, nitric oxide, gasotransmitters, and methylene blue, diluted in 250 ml of normal saline. A total of 73 infusion sessions were administered with a titration schedule adjusted to clinical response and tolerance: oxyhydrogen (HHO) 5–50 ml, nitric oxide (NO) 2.5–10 ml, gasotransmitters (GT) 2.5–10 ml, and methylene blue (MB) 0.5–1 ml per session. This therapy was provided alongside standard lipid-lowering treatment with atorvastatin (Lipitor) 10 mg once daily. The patient also received comprehensive education and counseling on cardiovascular health, emphasizing dietary optimization, physical activity, stress management, and adherence to prescribed medications and infusion schedules to maximize therapeutic benefits and support long-term vascular health.

2.6. Follow-Up and Outcomes

The patient showed significant clinical improvement, with complete resolution of angina and dyspnea and a marked increase in functional capacity. Initial coronary angiography in 2023 showed a calcium score of 0, with the left main artery normal. The mid-segment of the left anterior descending

artery (LAD) had soft plaque with mild to moderate stenosis (40–60%), while the proximal and distal segments had minimal stenosis (<25%). The left circumflex artery (LCx) was normal, and the right coronary artery (RCA) was dominant with minimal stenosis (<25%). A repeat angiography on August 7, 2025, showed clear improvement. The left main and LCx arteries remained normal. The LAD mid-segment stenosis decreased to only 20–30%, and the RCA mid-segment showed just 10–20% stenosis. Laboratory results also showed favorable lipid and inflammatory profiles: total cholesterol decreased from 167 mg/dL (11/2024) to 165 mg/dL (08/2025), LDL stayed stable at 55 mg/dL, HDL remained high at ~100 mg/dL, and triglycerides dropped from 62 to 58 mg/dL. ApoA1 was 2.16 g/L, ApoB was 0.44 g/L, with an excellent ApoB/A1 ratio of 0.20, and lipoprotein(a) stayed below 7 mg/dL. Inflammatory and cardiac markers, including hs-CRP (1.70 mg/L), hs-troponin (9.8 ng/L), CK (199 U/L), and CK-MB (3.90 ng/mL), remained within safe ranges. Additionally, renal function showed slight improvement, with eGFR rising from 89 to 93 mL/min/1.73 m². No serious adverse events were reported, and only mild, transient reactions occurred, all of which were easily managed.

3. Discussion

The patient’s marked clinical recovery, with resolution of angina and dyspnea and improved functional capacity, is consistent with improved symptoms but does not by itself establish better myocardial perfusion or a reduced ischemic burden. Imaging findings further support this clinical improvement: the estimated mid-segment stenosis in the LAD decreased from 40–60% to 20–30%. However, the RCA estimates of <25% at baseline and 10–20% at follow-up overlap, and these imaging findings cannot definitively establish plaque regression or stabilization without standardized serial imaging and quantitative plaque analysis [3]. These changes, combined with stable or improved lipid and inflammatory profiles, suggest the therapeutic potential of nanobubble and gasotransmitter therapy in enhancing endothelial function, reducing microvascular obstruction, and promoting vascular healing. No adverse events were documented during the reported treatment period, although this single observation cannot establish safety.

Nanobubbles are ultra-small gas-filled particles, generally less than 1 µm and commonly ranging from tens to hundreds of nanometers, with unique properties—including high internal pressure, a large surface-to-volume ratio, and relative stability—that make them potential carriers for therapeutic gases [8,9]. These properties may enable them to circulate longer and deliver oxygen more effectively to microvascular and hypoxic tissues, potentially improving perfusion and oxygenation [8–10]. However, whether intravenously administered nanobubbles improve perfusion or oxygenation in ischemic human coronary vessels remains uncertain [9,10].

Bioactive gases such as molecular hydrogen (H₂), together with endogenous gasotransmitters such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S), are involved in maintaining vascular homeostasis by regulating endothelial function, promoting vasodilation, and controlling oxidative stress and inflammation [10,11]. When delivered—particularly when incorporated within nanobubbles—these gases may enhance gas transport and endothelial signaling and decrease vascular inflammation [9–11]. However, their contribution to the stabilization or regression of soft atherosclerotic plaques in humans has not been established [10,11].

Methylene blue (MB) may provide several biological effects potentially relevant to coronary artery disease by enhancing mitochondrial function, maintaining vascular tone, and reducing oxidative stress. Acting as an alternative electron carrier, MB can transfer electrons from NADH directly to cytochrome c, bypassing dysfunction in mitochondrial complexes I and III. This process may support ATP production and mitochondrial respiration in experimental systems, although its clinical benefit in ischemic heart tissue has not been established [13]. Additionally, MB functions as a soluble guanylate cyclase (sGC) and nitric oxide synthase inhibitor, counteracting excessive nitric oxide-induced vasodilation and aiding in the restoration of vascular tone. However, this mechanism does not establish a therapeutic benefit in stable CAD [12]. MB has also demonstrated antioxidant effects by reducing lipid peroxidation and oxidative and nitrosative stress in an animal model of cardiac ischemia and reperfusion [12]. Importantly, these cardiac effects were dependent on the

timing of administration, with both cardiotoxic and cardioprotective effects reported in the animal model [12].

Compared with standard treatments, nanobubble combined with gasotransmitter therapy has been proposed to offer systemic advantages—such as improving microvascular oxygen delivery, decreasing oxidative stress, and enhancing endothelial function—rather than providing anatomical revascularization [9–11]. However, these proposed advantages remain hypothetical and cannot be established from this case. PCI alleviates ischemia caused by focal flow-limiting lesions, whereas CABG is effective for selected patients with complex or multivessel disease [4]. Statins help stabilize plaques and may achieve modest regression, while antiplatelet therapy reduces the risk of thrombotic cardiovascular events; however, these treatments do not consistently produce substantial anatomical plaque regression [3,4]. In this case, the observed decrease in estimated stenosis cannot be considered more rapid or extensive than that achieved with drug therapy alone because atorvastatin and lifestyle counseling were provided concurrently, there was no control group, and the baseline and follow-up imaging examinations were performed approximately 23 months apart. Nevertheless, the findings support the hypothesis that nanobubble treatment may serve as a complement to current approaches, although larger controlled clinical trials are necessary to confirm its effectiveness.

This report is based on a single patient's case, which limits its applicability to a broader population. Factors such as individual variability, concurrent medication—including atorvastatin—lifestyle influences, and the natural course of the disease may have played a role in the observed improvements. The lack of a control group makes it difficult to definitively link the clinical and imaging outcomes to nanobubble therapy. To validate these results, confirm safety, and develop standardized treatment protocols, larger controlled clinical trials are necessary.

Future research should focus on conducting well-designed randomized controlled trials to evaluate the efficacy and safety of nanobubble therapy in patients with coronary artery disease. These studies should compare standard treatment plus nanobubble therapy with standard treatment alone, without withholding clinically indicated PCI or CABG, using clinical outcomes, standardized imaging data, objective ischemia or perfusion assessments, and biomarker analysis as endpoints. Additionally, dose–response relationships, long-term effects, and mechanisms of action—including microcirculation improvement, endothelial modulation, and plaque remodeling—should be thoroughly investigated to establish standardized treatment protocols.

4. Conclusions

In this patient with CAD, adjunctive oxyhydrogen- and gasotransmitter-containing nanobubble infusions were temporally associated with resolution of exertional symptoms and a lower estimated degree of stenosis on follow-up coronary imaging. Because this was a single uncontrolled observation with concomitant statin therapy and incompletely standardized imaging, efficacy and causality cannot be inferred. The case supports further hypothesis-driven investigation with reproducible intervention specifications, standardized imaging, and prospective safety assessment.

5. Patient Perspective

Before starting the therapy, I only felt chest discomfort and shortness of breath when exercising or doing heavier activities. As the therapy went on, those symptoms slowly disappeared. Now, I can exercise and stay active without worrying about angina or getting out of breath. I also feel more energized in my daily life, and the treatment itself was smooth—I did not experience side effects or discomfort during the sessions.

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Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper and the accompanying clinical data.

Data Availability Statement: The clinical data underlying this report are not publicly available because of patient privacy and confidentiality requirements. De-identified information may be made available by the corresponding author upon reasonable request, subject to applicable ethical and privacy restrictions.

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Abbreviations

The following abbreviations are used in this manuscript:

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
CCTA	Coronary CT angiography
CK	Creatine kinase
CK-MB	Creatine kinase-MB
CO	Carbon monoxide
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
GT	Gasotransmitters
H ₂	Molecular hydrogen
H ₂ S	Hydrogen sulfide
HDL	High-density lipoprotein
HHO	Oxyhydrogen
hs-CRP	High-sensitivity C-reactive protein
LAD	Left anterior descending artery
LCx	Left circumflex artery
LDL	Low-density lipoprotein
MB	Methylene blue
NB	Nanobubble
NO	Nitric oxide
NYHA	New York Heart Association
O ₂	Molecular oxygen
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
sGC	Soluble guanylate cyclase

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