JACC: CASE REPORTS
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION.

VOL. 3, NO. 9, 2021

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Coronary Artery Vasospasm Requiring Cardiac Autotransplantation Yet Controlled With Tobacco

Matthew V. Tran, MD,[a,b] Eric Marceau, BS,[a,b] Yu Liu, PhD,[a] Karim Sallam, MD,[a,b,c] Pedro Medina, BS,[a,b] Chun Liu, PhD,[a] Nazish Sayed, MD, PhD,[a] Matthew D. Muller, PhD,[d] David H. Liang, MD, PhD,[c] Ian Y. Chen, MD, PhD[a,b]

ABSTRACT

Coronary artery vasospasm is typically managed through avoidance of triggers and with symptomatic treatments with calcium channel blockers and long-acting nitrates. Here, we report a rare case of medically refractory coronary artery vasospasm associated with genetic predispositions that initially required cardiac autotransplantation followed paradoxically by nicotine for long-term symptomatic control. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:1177–81) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 44-year-old White man presented to our clinic (Stanford Health Care, Stanford, California) for a second opinion regarding his chest discomfort. Two years before his presentation, he experienced chest pain while lecturing at work, and after prompt evaluation at a local hospital, he was found to have an inferior ST-segment elevation myocardial infarction, for which he received tissue plasminogen activator. He subsequently underwent coronary angiography, which reportedly showed normal coronary arteries, and left ventriculography, which showed hypokinesis in the basal inferior wall but no apical ballooning. After the myocardial infarction, he quit smoking cigarettes but began to experience recurrent resting chest pain often triggered by cold and emotional stress. He was empirically treated for vasospastic angina with calcium channel blockers (CCBs) and long-acting nitrates, but his symptoms persisted.

LEARNING OBJECTIVES

- To consider increased genetic susceptibility in patients with CAV unresponsive to medical therapies.
- To understand the limitation of cardiac autotransplantation in providing long-term symptomatic control for medically refractory vasospastic angina secondary to autonomic reinnervation.
- To recognize that nicotine, generally avoided as a trigger for CAV, can very rarely and paradoxically provide symptomatic relief following cardiac autotransplantation by unknown mechanisms.

From the [a]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California, USA; [b]Medical Service, Cardiology Section, Veterans Affairs Palo Alto Health Care System, Palo Alto, California, USA; [c]Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA; and the [d]Department of Anesthesiology and Perioperative Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 28, 2020; revised manuscript received March 18, 2021, accepted March 25, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.03.018

ABBREVIATIONS AND ACRONYMS

CAV = coronary artery vasospasm

CCB = calcium channel blocker

PAST MEDICAL HISTORY

His past medical history was significant for dyslipidemia and a 32-pack-year tobacco smoking history.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included mainly vasospastic angina and microvascular angina.

INVESTIGATION

At our institution, the patient underwent coronary angiography with acetylcholine challenge. At baseline, he was found to have diffuse narrowing of all branches of his left anterior descending and left circumflex arteries and severe diffuse vasospasm of his right coronary artery, which worsened with intracoronary acetylcholine but resolved with intracoronary nitroglycerin (**Figures 1A to 1F**). During the acetylcholine challenge, he had chest discomfort and diffuse T-wave abnormalities on electrocardiography that resolved with intracoronary nitroglycerin. A repeat angiogram 2 years later after medical therapies had failed (see later text) showed similar findings, except that coronary flow reserve in the left anterior descending artery was 7.4. Recently, whole-exome sequencing of his peripheral blood mononuclear cells as a part of an approved research study showed multiple genetic variants previously associated with coronary artery vasospasm (CAV) (**Table 1**) (1–3).

MANAGEMENT

On the basis of his history of atypical angina and angiographic findings, our patient was given a diagnosis of CAV and vasospastic angina. In addition to up-titration of his CCB (nifedipine and diltiazem) and long-acting nitrate (isosorbide mononitrate) to at least moderate doses (with higher doses limited by hypotension), he was tried on nicorandil, statins, L-arginine, magnesium supplementation, and bilateral stellate ganglion block, without relief. Despite adherence to medications, he continued to have daily angina leading to frequent hospital visits every 3 weeks, with myocardial infarction ruled out each time and myocardial ischemia ruled out by numerous imaging stress tests. Eventually, he underwent cardiac autotransplantation for complete denervation and symptomatic relief.

Unfortunately, his angina recurred 9 months post-transplantation. Although it was less intense and more sporadic than previously, it could not be controlled with antianginal agents. He had 2 serious anginal episodes, 1 leading to hospitalization for a nitroglycerin infusion and the other sustained ventricular tachycardia, for which he received an implantable cardioverter-defibrillator. Eventually, out of desperation, he underwent a trial of nicotine patch for the sheer possibility that CAV had developed after he quit smoking. Unexpectedly, he gained significant relief and was able to discontinue all antianginal agents. He later switched to smoking cigars because of skin hypersensitivity to the nicotine patch.

DISCUSSION

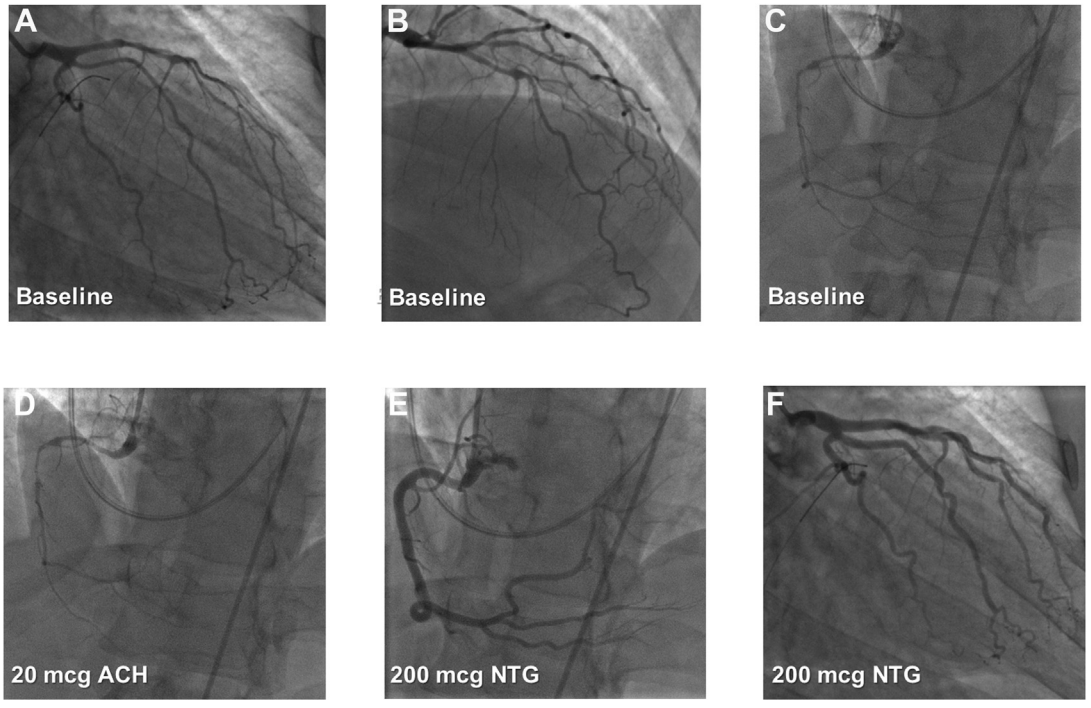
CAV is characterized by intense focal or diffuse vasoconstriction of epicardial coronary arteries leading to angina (vasospastic angina). Male patients and those 40 to 70 years old are most affected. Smoking is a significant risk factor and trigger for this condition (4). Other triggers include emotional stress, cold, stimulants, magnesium deficiency, hyperventilation, and certain medications (e.g., nonselective β-blockers, which our patient was not taking). Our patient's age, male sex, smoking, and triggers are all consistent with CAV.

CAV is diagnosed by coronary angiography, during which spontaneous epicardial vasospasm can be observed or, if not, elicited with provocation (acetylcholine or ergonovine). Concurrent angina and electrocardiographic evidence of ischemia during provocation and their resolution with intracoronary nitroglycerin are best for fully diagnosing CAV. Although microvascular dysfunction often coexists with this condition, this was not the case for our patient, whose coronary flow reserve exceeded 2 (cutoff for diagnosis).

Our patient's severe CAV could not be attributed to his tobacco use alone and may be potentiated by multiple genetic variants that made him particularly susceptible to CAV. These variants are related to vasoconstriction (endothelin-1), lipid transport (apolipoprotein E), and inflammatory cell trafficking (rho guanosine triphosphatase–activating protein-9), thus supporting the notion that CAV arises from both defects in vasomotor function and derangements that irritate the vasculature. The selective design of medical therapy on the basis of genetic variants, although not clinically routine, may hold promise for future treatment of refractory CAV.

Current medical therapies for CAV include CCBs and long-acting nitrates as first-line agents. When these agents fail, statins, magnesium supplements, nicorandil, and L-arginine can be used with variable success. In the case of medically refractory angina,

FIGURE 1 Coronary Angiography



Selective left coronary angiography reveals diffuse narrowing of **(A)** the left circumflex artery, **(B)** the left anterior descending artery, and their respective branches. **(C)** Selective right coronary angiography reveals severe diffuse vasospasm of right coronary artery, which **(D)** worsens after intracoronary acetylcholine (ACH) and **(E)** resolves after intracoronary nitroglycerin (NTG). **(F)** Nitroglycerin also vasodilates all major vessels in the left coronary circulation.

coronary stenting (focal spasms) and stellate ganglion blocks or sympathectomy can occasionally provide relief. In extreme cases, cardiac autotransplantation with complete denervation can be performed to inhibit vasospasm and pain sensation, but its long-term efficacy is limited by autonomic reinnervation post-transplantation, as previously suggested (5). Our case further demonstrates that nicotine use post-transplantation may paradoxically alleviate CAV.

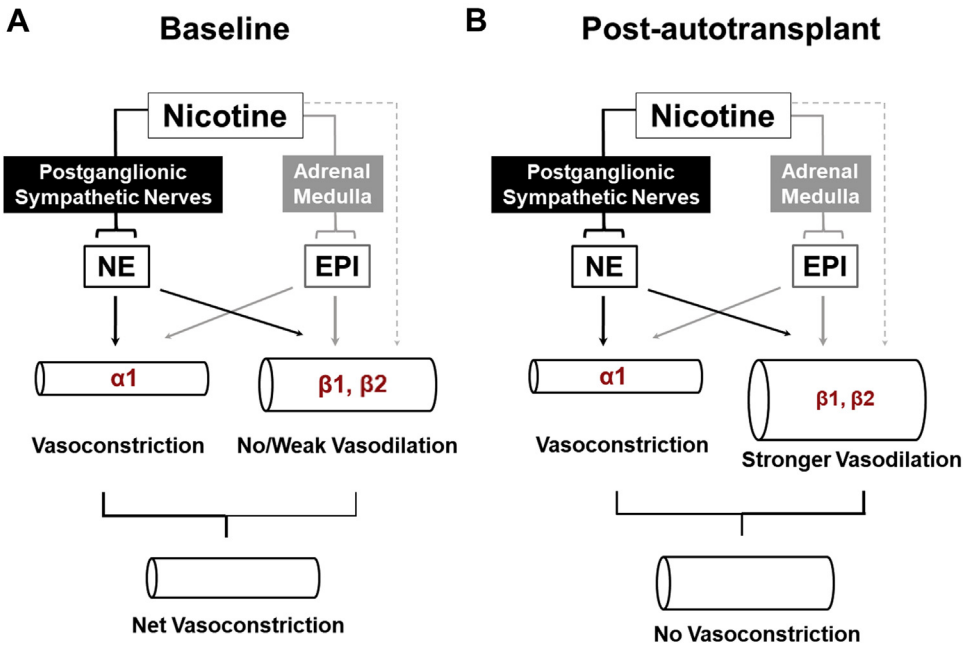
The reasons for our patient's symptomatic relief from the nicotine patch and cigars after cardiac autotransplantation remain enigmatic, but they may be related to an altered coronary vasomotor response to nicotine (**Figures 2A and 2B**), which is typically associated with increased sympathetic and blunted parasympathetic activities. Although the general net effect of nicotine is vasoconstrictive with a propensity for increased vasospasm, there exist conditions that may allow our patient to respond differently: 1) he had a heart transplant, which is known to cause a shift of β_1- to β_2-adrenoreceptor expression in the myocardium (6) that, if extending to the coronary arteries, would make epicardial vessels (predominantly β_1) under greater β_2-adrenoreceptor control, thus favoring vasodilation; 2) nicotine can directly activate β_2-adrenoreceptors (7) to induce epicardial vasodilation if a β_1-to-β_2 switch post-heart transplantation is substantial; 3) nicotine can increase adrenal release of epinephrine levels (7) to bias β_2-mediated vasodilation; 4) our patient's parasympathetic reinnervation post-transplantation is incomplete, as evidenced by his elevated baseline

TABLE 1 Patient's CAV-Related Genetic Variants

Gene Name	Genetic Variant	Accession Number	Patient Allele	Ref. #
Apolipoprotein E *(APOE)*	-219G>T	rs405509	G | T	(1)
Endothelin 1 *(EDN1)*	5665G>T (Lys198Asn)	rs5370	G | T	(2)
Rho GTPase-activating protein 9 *(ARHGAP9)*	1108T>G (Ala370Ser)	rs11544238	T | G	(3)
Rho GTPase-activating protein 9 *(ARHGAP9)*	A>G (Thr449Ala)	rs2277315	A | G	(3)

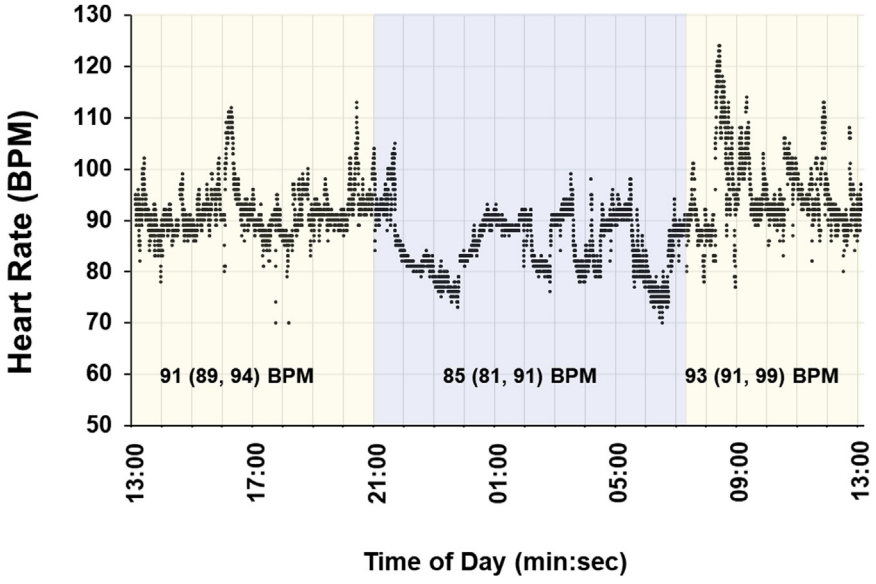
CAV = coronary artery vasospasm; GTPase = guanosine triphosphatase.

FIGURE 2 Normal and Altered Vasomotor Response to Nicotine



(A) Nicotine normally binds to postganglionic sympathetic nerves innervating the coronary vasculature, thus leading to locally increased norepinephrine (NE). Sympathetic activation of the adrenal medulla further increases circulating epinephrine (EPI). Catecholamine-mediated activation of α_1- and β_2 (more than β_1)-adrenoreceptors within epicardial arteries (>400 μm; composed of mostly α_1 and β_1) leads to vasoconstriction and vasodilation, respectively. Additionally, catecholamine-mediated activation of β_1-adrenoreceptors in the heart causes increased heart rate and contractility, leading to metabolic and increased flow-mediated dilation (not shown). Nicotine can also directly activate β-adrenoreceptors **(dashed arrow).** The relative adrenoreceptor density is indicated in **red** by font size. **(B)** Our patient likely had greater β_2-adrenoreceptor–mediated vasodilation in response to nicotine because of his heart transplant (β_1-to-β_2 switch).

FIGURE 3 Ambulatory Heart Rate Monitoring (Fitbit HR, Fitbit, San Francisco, California)



Median (interquartile) heart rates were indicated for awake **(yellow)** and sleep **(blue)** periods. BPM = beats/min.

awake heart rate during ambulatory recording (**Figure 3**), thus limiting the potential for vagally mediated (rather than entirely sympathetically mediated) vasospasm (8). Because the initiation of CAV involves coordinated autonomic modulation or dysregulation, alterations in both the autonomic circuitry (8) and the post-synaptic adrenoreceptor characteristics may have contributed to our patient's paradoxical response to nicotine and cigars.

FOLLOW-UP

The patient was able to remain symptom-free on cigars for more than 14 years except for 1 hospitalization requiring intravenous nitroglycerin treatment.

CONCLUSIONS

CAV is a multifactorial disease involving not only defects in the components of the coronary vasculature but also alterations in the autonomic modulation of vasomotor function. Although nicotine is an adverse trigger for CAV, its effect on coronary vasomotor tone (and vasospastic tendency) can be altered by patient-specific factors (e.g., genetics, autonomic denervation). Further research into the interplay between nicotine and patient-specific factors may provide the mechanistic insight needed to develop new therapeutics to treat resistant CAV.

ACKNOWLEDGMENT The authors would like to thank Dr. Pei-Yu Lee for her assistance with manuscript preparation and the patient for generously sharing his ambulatory heart rate recording.

FUNDING SUPPORT AND AUTHOR DISCLSOSURES

This study was supported in part by the American Heart Association Career Development Award (AHA 18CDA34110047) and the Stanford Translational Research and Applied Medicine (TRAM) Center Pilot Grant. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESSES FOR CORRESPONDENCE: Dr. Ian Y. Chen, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Avenue, Suite 111C, Palo Alto, California 94304, USA. E-mail: iychen@stanford.edu. OR Dr. David Liang, Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Room H-2157, MC5233, Stanford, California 94305-5233, USA. E-mail: dliang@stanford.edu. Twitter: @IanChenMD.

REFERENCES

1. Murase Y, Yamada Y, Hirashiki A, et al. Genetic risk and gene-environment interaction in coronary artery spasm in Japanese men and women. Eur Heart J 2004;25:970–7.

2. Lee J, Cheong SS, Kim J. Association of endothelin-1 gene polymorphisms with variant angina in Korean patients. Clin Chem Lab Med 2008;46:1575–80.

3. Takefuji M, Asano H, Mori K, et al. Mutation of ARHGAP9 in patients with coronary spastic angina. J Hum Genet 2010;55:42–9.

4. Hung MJ, Hu P, Hung MY. Coronary artery spasm: review and update. Int J Med Sci 2014;11:1161–71.

5. Bertrand ME, Lablanche JM, Tilmant PY, Ducloux G, Warembourg H Jr., Soots G. Complete denervation of the heart (autotransplantation) for treatment of severe, refractory coronary spasm. Am J Cardiol 1981;47:1375–8.

6. Steinfath M, von der Leyen H, Hecht A, et al. Decrease in beta 1- and increase in beta 2-adrenoceptors in long-term follow-up after orthotopic cardiac transplantation. J Mol Cell Cardiol 1992;24:1189–98.

7. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: implications for electronic cigarette use. Trends Cardiovasc Med 2016;26:515–23.

8. Tan BH, Shimizu H, Hiromoto K, Furukawa Y, Ohyanagi M, Iwasaki T. Wavelet transform analysis of heart rate variability to assess the autonomic changes associated with spontaneous coronary spasm of variant angina. J Electrocardiol 2003;36:117–24.

KEY WORDS autonomic modulation, cardiac autotransplantation, coronary artery vasospasm, nicotine