Arrhythmogenic iatrogenesis imperfecta: A decades-long chase down the rabbit hole

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Introduction
A basic tenet of medicine is *primum non nocere*—“first, do no harm.” As physicians we do our best to carefully weigh the benefits and risks of therapies we offer to patients. When it comes to the performance of invasive procedures, experienced clinicians recognize that complications can arise even in the best of hands, and that sometimes such complications result in new problems requiring further treatments. Herein is presented an extraordinary case of a now 60-year-old patient who as a young adult suffered from the most common form of supraventricular tachycardia seen in practice—typical AV nodal reentrant tachycardia (AVNRT)—and whose clinical course over the years has been anything but typical.

Case report
Slowing down the AV node…but speeding up the SA node
The patient initially presented with recurrent episodes of symptomatic AVNRT during her early 20s in the era prior to the routine availability of minimally invasive catheter ablation. At the time, her symptoms occurred 1–2 times per month, with documented rates up to 230 beats per minute (bpm). After failing attempts at pharmacologic management, she underwent a cryosurgical modification of her atrioventricular node in 1986—at the time a relatively new treatment and the only nonpharmacologic option available apart from placement of a permanent pacemaker with concurrent AV node ablation. Indeed, she was “Patient No. 6” in the seminal case series published by Cox and colleagues1 initially describing their results with this novel surgical technique.

She had no further episodes of AVNRT and did well in early follow-up; however, she developed persistent sinus tachycardia, which over time became progressively symptomatic. She was ultimately diagnosed with inappropriate sinus tachycardia secondary to iatrogenic vagus nerve injury sustained during her surgery. Attempts at pharmacologic management were met with limited success, and by 2002 her symptoms had progressed to the point that she opted to undergo further invasive therapies.

Swapping sinus tachycardia for sinus node dysfunction
In early 2002 she underwent a catheter-based sinus node modification, which proved unsuccessful. Later that summer she underwent a second catheter-based sinus node modification, which acutely resulted in severe bradycardia owing to sinus node dysfunction. She underwent placement of a single-chamber AAIR pacemaker utilizing a Guidant FineLine II Sterox EZ 4469 pacing lead (Guidant Corporation, Indianapolis, IN) and a Guidant Insignia Plus SR 1194 pulse generator; however, within weeks of her procedure she again developed recurrent symptomatic sinus tachycardia, and in late summer she underwent a third catheter-based attempt to abolish all sinoatrial node function. She again failed to achieve lasting relief from her symptoms, and in late 2002 ultimately underwent an open surgical isolation and cryogenic ablation of her sinoatrial node: she was “Patient No. 7” in the published surgical series by Khiabani and colleagues2 describing their experience with this procedure.

KEY TEACHING POINTS
- Some complications of cardiac ablations may not manifest themselves for months or even years following a procedure.
- Patients undergoing repeat procedures may be at increased risk of complications resulting from the cumulative effects of extensive cardiac substrate modification.
- Biatrial pacing may be effective in ameliorating symptoms in patients with iatrogenic interatrial dissociation.

KEYWORDS
- Atrioventricular nodal reentrant tachycardia
- Biattrial pacing
- Complete heart block
- Cryosurgical ablation
- Ectopic atrial tachycardia
- Inappropriate sinus tachycardia
- Interatrial dissociation
- Pacemaker-mediated tachycardia
- Pacemaker syndrome
- Vagus nerve injury

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She did well from an arrhythmia standpoint for nearly a decade thereafter except for infrequent episodes of vasodepressor syncope, with her only intervention during this period being a pulse generator replacement that was carried out in 2011 with placement of a Boston Scientific Altura 60 S061 (Boston Scientific, Marlborough, MA) pulse generator.

The incessant atrial tachycardias
In late 2012 she presented with recurrent symptomatic atrial tachyarrhythmias at rates between 110 and 160 bpm. Initially reluctant to pursue a trial of pharmacologic therapy owing to its past ineffectiveness with her inappropriate sinus tachycardia, she opted for an electrophysiology study (EPS). She was found to have multiple ectopic foci located along the inferior aspect of the crista terminalis, the coronary sinus ostium, and the left side of the interatrial septum, all of which were successfully ablated intraoperatively (although a junctional tachycardia remained inducible, no attempt was made to ablate this). Unfortunately, almost immediately after her procedure she developed recurrent atrial tachyarrhythmias at rates up to 140 bpm. Her propensity for such incessant ectopic atrial tachycardias was thought to be a late-term sequela of her long-standing unopposed cardiac sympathetic stimulation resulting from her old vagus nerve injury. Over the next several months attempts at pharmacologic suppression with various beta-blockers, calcium channel blockers, class IC and class III antiarrhythmic drugs, and centrally acting sympatholytics were either ineffective or not tolerated owing to side effects. Although the option of a surgical cardiac sympathetic denervation was entertained, this was decided against owing to the lack of clinical data supporting its efficacy in this clinical situation. During this period, her pacemaker exhibited intermittent sensing issues owing to low P-wave amplitudes and far field R-wave oversensing.

After exhausting pharmacologic options, she underwent a repeat EPS and permanent pacemaker system revision in early 2014. An ectopic focus mapped to the superolateral aspect of the mitral valve annulus was successfully ablated, as was a second ectopic focus via microreentrant circuit localized to the interatrial septum (the tachycardia was noted to consistently terminate with overdrive atrial pacing). No intra-procedure AV block was seen at any time, and intact 1:1 AV conduction was documented post ablation with overdrive atrial pacing at rates up to 200 bpm. Owing to the aforementioned atrial sensing issues, her pacemaker system was upgraded with placement of 2 new Medtronic CapSureFix Novus 5076 (Medtronic, Minneapolis, MN) leads in the right atrium and ventricle (with capping of her old atrial lead) and a replacement of the pulse generator with a Medtronic Advisa DR MRI A2DR01 SSR model with support for atrial anti-tachycardia therapies. The decision for a dual-chamber upgrade proved prescient: at follow-up 4 weeks later she was found to be in complete heart block.

Pacemaker-mediated tachycardia in the setting of not-so-complete heart block
In the 5 years that followed, she did well from an arrhythmia standpoint, although she continued to have episodes of vasodepressor syncope as well as clinical manifestations of diastolic heart failure, which was managed with diuretics. Infrequent runs of atrial tachycardia were documented via her device, but these were consistently terminated by atrial anti-tachycardia pacing and were largely asymptomatic after her development of complete anterograde heart block (which never resolved). She reported having some new exertional limitations with certain activities such as riding a stationary bike, presumably owing to the loss of the minute ventilation component of Boston Scientific’s blended sensor; otherwise, she remained very active and participated in moderate-intensity sports such as pickleball.

In early 2019 she presented with new symptoms of exercise intolerance and episodes of paroxysmal exercise-induced tachycardia: she specifically described sudden increases in her heart rate with mild-to-moderate activity up to her device’s maximum programmed tracking rate. Treadmill exercise testing confirmed periods of pacemaker-mediated tachycardia (PMT) secondary to exercise-induced retrograde VA conduction. Although PMT was effectively eliminated through extension of her postventricular atrial refractory period, she continued to have exercise intolerance owing to episodes of repetitive nonreentrant ventriculoatrial synchrony. Efforts at suppressing both PMT and repetitive nonreentrant ventriculoatrial synchrony programmatically were either ineffective or required setting upper sensor rate limits that were poorly suited to her activity level. Attempts at pharmacologic nodal blockade also proved ineffective. She ultimately underwent an AV node ablation with the goal of definitively abolishing all residual retrograde AV nodal conduction.

Variant pacemaker syndrome owing to interatrial dissociation
She noted an immediate improvement in her exercise capacity following her AV node ablation; however, over the next several months, she reported intermittent episodes of her “chest pounding,” with associated symptoms of dyspnea lasting several minutes to hours at a time. Her symptoms occurred both at rest and with exertion, without any obvious precipitating factors, and became increasingly more frequent. Echocardiography performed while she was having symptoms demonstrated normal left ventricular systolic function with a normal global longitudinal strain pattern; however, she was noted to have intermittent spontaneous P waves that were dissociated from right atrial pacing. Her transmirtal Doppler profile revealed that those electrocardiographic ectopic P waves were associated with her sonographic left atrial A waves, which were otherwise absent despite the presence of a right atrial paced P wave (Figure 1). These findings suggested electrical dissociation between the left atrium and the atrial territory that was controlled by her pacemaker.
An EPS was undertaken to ascertain the level of dissociation (ie, intra-atrial within the right atrium vs interatrial between the right and left atria). An Advisor HD Grid Mapping Catheter was used with EnSite Precision (Abbott Laboratories, Abbott Park, IL) to create detailed voltage and propagation maps of the right atrium and coronary sinus. These maps demonstrated extensive fibrosis along the interatrial septum (including around the ostium of the coronary sinus), as well as the right atrial posterior wall and floor. The right and left atria appeared to be completely dissociated at the level of the interatrial septum (Figure 2).

Her symptoms were felt to represent a variant of “pace-maker syndrome” owing to loss of left-sided atrioventricular synchrony (despite preserved right-sided atrioventricular synchrony), with her most recent ablation likely having inadvertently disrupted any remaining vestiges of connectivity between her right and left atria. Accordingly, a decision was made to upgrade her to a biatrial pacing system. An initial attempt at an endovascular approach was made using a Medtronic Attain Ability Plus 4296 bipolar coronary sinus (CS) lead placed into the CS. Left atrial pacing thresholds at multiple locations within the mid and distal CS body were inadequate, and lead stability in the proximal CS proved problematic. Ultimately, a small atrial branch was identified into which the distal tip of the CS lead was successfully wedged. The newly placed CS lead and the patient’s existing CapSureFix Novus right atrial lead were connected via a 2XBIS/BIS bifurcated IS-1 Y-connector (Oscor Medical, Palm Harbor, FL) to the atrial port of a new Boston Scientific Accolade MRI EL L331 pulse generator (the patient had opted to return to a device with a blended sensor); her right ventricular lead was connected to the pulse generator’s ventricular port. Intrinsic P-wave sensing was 3.0 mV, with biatrial capture achieved at 1.2 V @ 0.4 ms (confirmed via surface electrocardiogram). The following morning, there was loss of left atrial capture and the CS lead was found to have migrated on follow-up chest radiography. As placement of an active fixation lead within the CS just distal to its ostium was felt to be a poor option owing to the extensive fibrosis in this region, and owing to ongoing concerns with long-term lead stability with a passive fixation lead, a decision was made to pursue placement of an epicardial left atrial pacing lead.

The patient was brought to the operating room the following day, and 2 Greatbatch Epicardial 4046 (Integer Holdings Corporation, Plano, TX) bipolar leads were successfully placed along the dome of the left atrium via a mini-sternotomy. One of the leads was connected to the 2XBIS/BIS bifurcated IS-1 Y-connector after removal of the Attain Ability Plus coronary sinus lead. Biatrial capture was achieved at 1.6 V at 0.4 ms (confirmed via surface electrocardiogram) with an atrial sensitivity set to 0.25 mV. Her device lower rate limit was set to 85 bpm in order to suppress her competing ectopic atrial rhythm at rest.

She reported complete resolution of her symptoms after her recovery from surgery. At 12-month follow-up, she continued doing well and had returned to playing competitive pickleball. Only time will tell if this is the last chapter in her story.

Discussion
This case appears to be the first report of a patient developing late-term incessant ectopic atrial arrhythmias owing to longstanding unopposed cardiac sympathetic stimulation resulting from iatrogenic vagus nerve injury. In addition, although there have been other reports of interatrial dissociation among patients with extensive atrial fibrosis in the setting of atrial fibrillation/flutter, this appears to be the first report describing a patient developing symptomatic
pacemaker syndrome” owing to lack of left-sided atrioventricular synchrony despite preserved right-sided atrioventricular synchrony, with successful resolution of symptoms achieved with biatrial pacing. This is likely due to the fact that—unlike previously described patients with atrial fibrillation/flutter who likely had extensive left atrial fibrosis—this patient had relatively preserved left atrial contractility.

More generally, this case highlights the potential for adverse long-term consequences related to cardiac substrate modification for the treatment of cardiac arrhythmias. Although it would be easy to attribute this patient’s clinical course to the complication of a surgical procedure that is no longer routinely performed, it must be remembered that many of the complications suffered by this patient—from vagus nerve injury resulting in incessant sinus tachycardia,5 to the development of delayed heart block from progressive atrial fibrosis following septal ablation,6 to interatrial dissociation7—have all been described in contemporary case reports among patients undergoing catheter ablation procedures. Furthermore, atrial tachycardias are frequently observed after atrial fibrillation ablations—often the result of conduction gaps and nontransmural lesions—resulting in the replacement of one arrhythmia for another.8,9 Electrophysiologists must remain cognizant of the potential for unintentional and adverse late-term complications that may manifest themselves long after a patient has left the electrophysiology lab.

**Conclusion**

Herein is described the tortuous decades-long course of a patient in whom each well-intentioned attempt to correct one symptomatic arrhythmia resulted in another. Her case serves as a humbling reminder of the many advances in the field of cardiac electrophysiology over the past several decades—as well as its ongoing limitations.

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**Figure 2**  **A:** Surface and intracardiac electrograms (EGM) demonstrating electrical dissociation between the right and left atria. RA₉ and LA₉ denote the respective right atrial and left atrial surface EGM signals. RA, LA, and V denote the respective right atrial, left atrial, and ventricular intracardiac EGM signals. RAp and VAp denote the respective right atrial and ventricular pacemaker spikes. **B:** Voltage maps of the right atrium and coronary sinus, demonstrating extensive fibrosis along the interatrial septum (including around the ostium of the coronary sinus), as well as the right atrial posterior wall and floor.
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