Increasing pacemaker lead impedance and pacing threshold after initiation of chemotherapy with doxorubicin and cyclophosphamide

Daniel L. Varela, MD, Karnika Ayinapudi, MBBS, Bilal Ahmed, MD, Christopher A. Groh, MD, Roger A. Freedman, MD

From the Cardiology Division, University of Utah School of Medicine, Salt Lake City, Utah.

Introduction

Chemotherapy is a powerful tool used in cancer treatment. However, chemotherapeutic drugs come with a large host of side effects involving various organ systems. Cardiac side effects are common and include left ventricular systolic dysfunction, coronary artery disease, myocarditis, pericardial effusions, and arrhythmias. While certain drugs, such as some antiarrhythmic agents, can alter cardiac implantable electronic device (CIED) function, there is at present little evidence to suggest that chemotherapeutic drugs carry any risk of adverse effects on CIED function. We present a patient who experienced increasing pacemaker lead impedance and pacing threshold following initiation of chemotherapy with doxorubicin and cyclophosphamide.

Case report

A 68-year-old woman with a history of complete heart block status post implantation of a left-sided dual-chamber pacemaker 12 years prior presented to our institution following a syncopal episode. Chest radiography revealed appropriate pacemaker lead position without evidence of lead fracture (Figure 1). Electrocardiogram revealed an atrial sensed, ventricular paced rhythm with intermittent loss of ventricular capture (Figure 2). Interrogation of her Boston Scientific dual-chamber pacemaker revealed an estimated battery life of 4 years. There was a gradual increase in right ventricular (RV) lead (model: DEXTRUS #4137) impedance from 562 ohms to 1115 ohms and pacing threshold from 1.4 V @ 0.4 ms to 3.0 V @ 0.4 ms that began 6 weeks prior to presentation (Figure 3). Her right atrial lead parameters were normal and stable from prior (impedance 446 ohms from 493 ohms, threshold 0.3 V @ 0.4 ms from 0.4 V @ 0.4 ms, and P-wave sensing 6.9 mV from 7.6 mV). Repeat testing was performed with the RV lead in unipolar configuration, and the impedance improved to 346 ohms and the pacing threshold improved to 1.1 V @ 0.5 ms.

The patient was diagnosed with invasive ductal carcinoma of the right breast 3 months prior to presentation. She had not undergone any surgical or radiation-based treatments for her cancer, but had started treatment with doxorubicin and cyclophosphamide 6 weeks prior to presentation, and received her

KEY TEACHING POINTS

- Certain drugs, such as antiarrhythmic agents, can lead to pacemaker lead malfunction. Other drugs have a less clear effect on pacemaker lead function, though certain cardiotoxic drugs, such as the chemotherapeutic agents doxorubicin and cyclophosphamide, may interfere with normal pacemaker function.
- The mechanism by which chemotherapeutic drugs might affect pacemaker lead function is not well understood, but may be the consequence of these drugs' ability to cause endomyocardial fibrosis, which could create lead–myocardial tissue interface issues and lead to problems such as increasing pacemaker lead impedance and eventual loss of capture.
- Patients with pacemakers who undergo treatment with cardiotoxic agents may benefit from close electrophysiology follow-up after these drugs are initiated to help monitor for early changes in pacemaker function that might lead to clinically significant and potentially life-threatening device complications.

KEYWORDS Cardio-oncology; Cardiotoxicity; Chemotherapy; Cyclophosphamide; Doxorubicin; Pacemaker malfunction
(Heart Rhythm Case Reports 2022;8:845–848)

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Disclosures: The authors report that there are no conflicts of interest. There was no financial support provided to fund the preparation of this manuscript.
Address reprint requests and correspondence: Dr Daniel Varela, Division of Cardiology, University of Utah School of Medicine, 4th Floor, Room 4A100, 30 N 1900 E, Salt Lake City, UT 84132. E-mail address: daniel.varela@hsc.utah.edu.

https://doi.org/10.1016/j.hrcr.2022.09.011

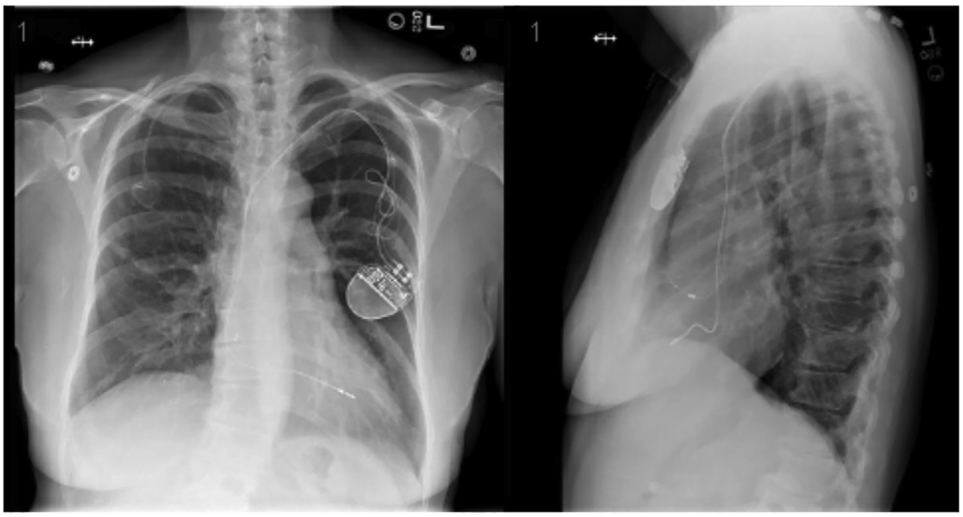

Figure 1 Chest radiograph revealing appropriate dual-chamber pacemaker lead position without radiographic evidence of lead fracture.

fourth cycle of chemotherapy (cumulative dose of doxorubicin 472 mg/m^2 and cyclophosphamide 4720 mg/m^2) 3 days before her syncopal episode. A transthoracic echocardiogram was performed to evaluate for signs of cardiotoxicity from her chemotherapy regimen. It revealed a slight increase in left ventricular size (left ventricular internal diameter in diastole of 5.6 cm, increased from 5.1 cm on last echocardiogram performed 1 week prior to starting chemotherapy). Other echocardiographic parameters, including left ventricular ejection fraction (54%), global longitudinal strain (-13%), RV size and function, and valvular function, remained unchanged. No pericardial effusion was visualized.

The patient's RV lead was left in unipolar configuration, and the pacing threshold was programmed at a fixed output at a 3× safety margin (3.5 V @ 0.5 ms). A discussion was held regarding possible placement of a new RV lead. The patient was under considerable stress owing to her recently diagnosed breast cancer, and she opted to pursue a noninvasive approach to managing her dysfunctional RV lead rather than undergo placement of a new lead (with or without extraction of her dysfunctional lead). This decision was

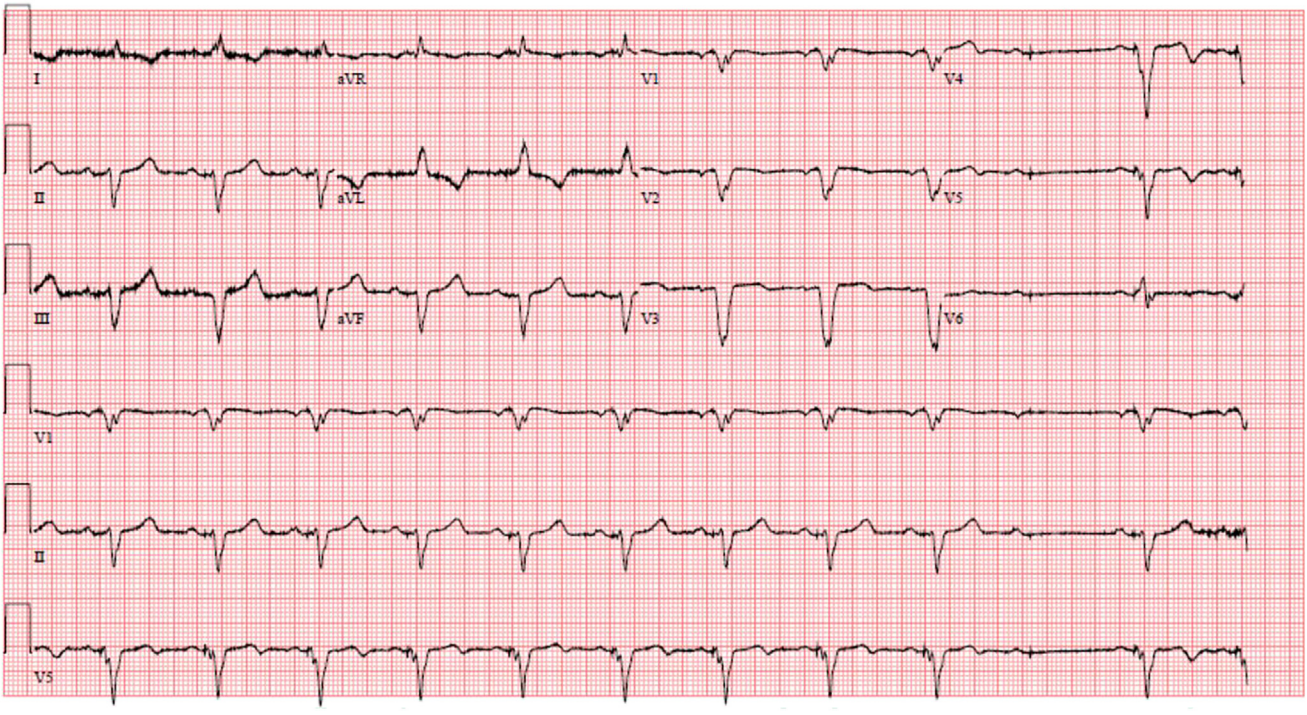

Figure 2 Electrocardiogram demonstrating an atrial sensed, ventricular paced rhythm with intermittent loss of ventricular capture.

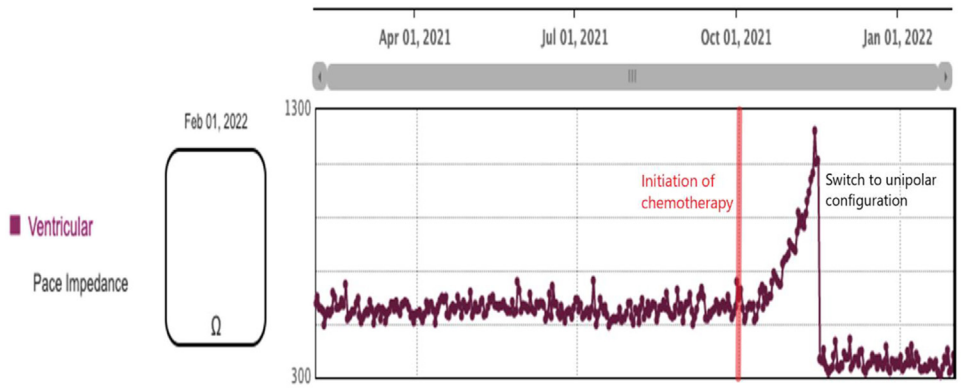

Figure 3 Device interrogation revealing an increase in right ventricular lead impedance shortly after initiation of chemotherapy with doxorubicin and cyclophosphamide.

also driven by the fact that she was actively undergoing treatment with chemotherapy and was concerned about increased risk of infection should she undergo placement of a new lead while receiving treatment. Concerns about what implications the placement of a new lead and the retention of the abandoned RV lead might have on her ability to undergo surveillance magnetic resonance imaging while on chemotherapy further supported the patient's decision to defer placement of a new RV lead until after she completed her immediate oncologic care.

The patient's oncologist subsequently switched her chemotherapy regimen to paclitaxel. Despite stopping doxorubicin and cyclophosphamide, repeat device interrogations continued to demonstrate an ongoing rise in RV lead impedance (from 1115 ohms to 1730 ohms) with stable pacing threshold in the bipolar configuration, until 3 months after hospital discharge, at which point bipolar testing could no longer be performed owing to immediate loss of capture when the RV lead was programmed back to the bipolar configuration. RV lead impedance and pacing thresholds have remained stable in the unipolar configuration following her initial hospitalization, and the patient has remained free of any syncopal events following hospital discharge.

Discussion

Potentially life-threatening issues can arise when pacemakers fail to function properly, as can occur when problems develop with the pacemaker battery or one of its leads. Pacemaker lead issues include lead dislodgement, presence of a loose set screw in the header block, lead insulation breach, conductor fractures, and lead–myocardial tissue interface issues such as endomyocardial fibrosis or scar formation. Pacemaker lead issues often initially manifest as abnormal changes in lead impedance, pacing threshold, or sensitivity. Lead noise may also be present in cases of lead insulation breach or conductor fractures. If detected early, these changes can prompt an evaluation for the underlying cause and allow the issues to be addressed before clinical signs and symptoms of pacemaker malfunction develop.

Chemotherapeutic drugs can cause several harmful effects on the heart. Anthracyclines, such as doxorubicin, are particularly well known for causing cardiotoxic side effects including dilated cardiomyopathy, myopericarditis, myocardial fibrosis, and arrhythmias in up to 11% of patients.[1,2] Alkylating agents, including cyclophosphamide, can cause myocarditis and heart failure.[3,4]

To date, little is known about the relationship between chemotherapeutic drugs, such as doxorubicin and cyclophosphamide, and pacemaker function. A single case report, presented by Wilke and colleagues[5] in 1999, described a 56-year-old woman with a history of pacemaker implantation and plasmacytoma who underwent 3 cycles of chemotherapy with vincristine, doxorubicin, and dexamethasone. Her pacing threshold was noted to have increased with each cycle of chemotherapy, though no comment was made regarding stability of pacemaker lead impedance. The patient's pacing thresholds remained stable after completion of chemotherapy.[5] To the best of our knowledge, no other cases of pacemaker lead dysfunction following initiation of chemotherapy have been described until now.

The reasons why our patient and the patient presented by Wilke and colleagues developed increasing pacing thresholds is unknown. However, one potential mechanism is the effect doxorubicin has on inducing endomyocardial fibrosis. Areas of scarred or fibrotic myocardium have been found in cardiac catheterization and electrophysiology labs to cause increased pacing thresholds during temporary pacemaker placement and diagnostic electrophysiology study.[6,7] If doxorubicin causes endomyocardial fibrosis, this may create lead–myocardial tissue interface issues that result in increased pacemaker lead impedance and pacing thresholds. Additionally, cyclophosphamide has been shown to cause various electrocardiogram changes, including diminished QRS complex voltage.[3,4] The mechanism by which cyclophosphamide causes decreased QRS voltage is unknown, but may play a contributing role in our patient's increasing pacing thresholds during her course of chemotherapy.

While we cannot confirm that the patient's increasing RV impedance and pacing thresholds were due to doxorubicin or cyclophosphamide, the fact that she had a documented trend

of stable lead parameters up until right after the initiation of chemotherapy raises suspicion that these events are related. The gradual onset of the patient's increasing RV lead impedance suggests that a biological process, such as a lead–myocardial tissue interface issue, was the cause for the change in lead parameters and makes a mechanical lead issue (eg, insulation breach or conductor fracture) unlikely, as mechanical lead issues tend to manifest with abrupt changes in lead impedance.[8] Lead noise, oversensing, and cross-talk can also result in the intermittent loss of capture that our patient's pacemaker experienced; however, these issues alone would not explain the patient's increasing lead impedance and pacing threshold, and the patient's device interrogation showed no evidence of these particular issues. Lead–myocardial tissue interface issues may affect 1 or both electrodes in a pacemaker lead, as scarred or fibrotic myocardium may develop around the lead ring electrode, the tip electrode, or both. Repeat lead testing in the unipolar configuration can help localize the site of injury, as lead parameters may either improve (if only the ring electrode is affected) or remain unchanged (if either the tip electrode or both the ring and tip electrodes are affected). Our patient's gradual increase in RV lead impedance and lack of noise supports that a biologic process, rather than a mechanical issue, led to the patient's lead dysfunction, while the improvement in lead impedance and pacing threshold when tested in the unipolar configuration suggests that the lead ring electrode was more catastrophically affected than the tip electrode, though the exact reasons why a potential chemotherapy-induced side effect (eg, endomyocardial fibrosis) would disproportionately affect a single-lead electrode remain unclear.

Despite discontinuing doxorubicin and cyclophosphamide, our patient's RV lead bipolar impedance continued to increase during follow-up, until bipolar testing was ultimately no longer able to be completed owing to immediate loss of RV capture. This finding contrasts with the patient presented by Wilke and colleagues, where lead impedance remained stable after discontinuation of vincristine and doxorubicin. Risk of cardiotoxicity is greatest at increasing cumulative drug doses, particularly among patients who receive >400–500 mg/m^2 of doxorubicin.[2] One study[9] found that cardiotoxicity occurred in 25% of patients who receive cumulative doses >500 mg/m^2, 50% of patients who receive >600 mg/m^2, and almost all patients who receive >800 mg/m^2. Our patient received a cumulative 472 mg/m^2 dose, which would place her at risk of cardiotoxic drug effects. The patient presented by Wilke's group received a lower dose (reported at 108 mg/m^2), and perhaps differences in cumulative dose between the 2 patients might explain why one demonstrated improvement in lead impedance after drug discontinuation, while the other did not.

Our patient was offered placement of a new RV lead vs close serial monitoring of her existing RV lead. After discussion of an RV lead revision or extraction procedure, her preference, in conjunction with the adequacy and stability of RV lead performance in a unipolar configuration, was to first focus her treatment on her active malignancy with a goal of pursuing lead extraction after completion of her immediate oncologic care.

Conclusion

Little is known about the role chemotherapy and other cancer treatments play on pacemaker function; and while much remains to be learned, the present case suggests that patients with CIEDs treated with cardiotoxic agents may benefit from close electrophysiology follow-up after treatment initiation to help monitor for any changes in pacemaker function and allowing these changes to be detected early, before progression to clinically significant and potentially life-threatening device complications occurs. Close monitoring in the electrophysiology clinic for cancer patients with CIEDs may become increasingly important in the future, as newer chemotherapeutic and immunomodulating agents with unknown side effect profiles continue to be developed and used for the treatment of oncologic conditions.

References

1. Chatterjee K, Zhang J, Honbo N, Karliner JS. Doxorubicin cardiomyopathy. Cardiology 2010;115:155–162.
2. Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. Prog Cardiovasc Dis 2007;49:330–352.
3. Kumar S, Gupta RK, Samal N. Cyclophosphamide cardiotoxicity. Natl Med J India 1992;5:17–19.
4. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med 1981;141:758–763.
5. Wilke A, Hesse H, Gorg C, Maisch B. Elevation of the pacing threshold: a side effect in a patient with pacemaker undergoing therapy with doxorubicin and vincristine. Oncology 1999;56:110–111.
6. Clark JG, Bucheleres G, Carleton RA. Endocardial fibrosis: detection by cardiac pacing. Circulation 1968;38:1136–1139.
7. Sundaram C, Kartik SV, Namboodiri N, Ajitkumar VK. A novel pacing option in patients with endomyocardial fibrosis: a case series. Indian Pacing Electrophysiol J 2021;21:303–307.
8. Swerdlow CD, Koneru JN, Gunderson B, Kroll MW, Ploux S, Ellenbogen K. Impedance in the diagnosis of lead malfunction. Circ Arrhythm Electrophysiol 2020;13:e008092.
9. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710–717.