

## EDITORIAL COMMENT

# Anthracycline-Induced Vascular Dysfunction

## Is MitoQ the Answer?\*

Douglas B. Sawyer, MD, PhD



Anthracycline antibiotics have been in use for more than half a century in the treatment of cancer and the dose-limiting cardiovascular toxicity has been recognized for most of that time. Despite this and other toxicities, anthracyclines continue to be important components of chemotherapy for both solid and hematologic malignancies. There has been a great deal of effort put into understanding the mechanisms for the cardiovascular toxicity of anthracyclines and development of strategies to limit the adverse effects, while not interfering with the antitumor efficacy. Preclinical models have been used extensively, and many rodents have been sacrificed in the hopes of making anthracyclines a safer class of medications for humans. Clayton et al. (1) have added to that effort and in an elegant set of experiments advance the concept that protection of vasculature with repletion of mitochondrial coenzyme Q10 could be the answer to this age-old question.

The effects of anthracyclines on mitochondrial function with increased generation of oxidant stress are well established, including the effect on mitochondrial coenzyme Q10 synthesis (2). This has led to clinical studies examining whether coenzyme Q10 repletion can prevent cardiotoxicity (3). What is novel

in the work from Clayton et al. (1) is the use of modified coenzyme Q10 that is predominantly taken up into mitochondria – “MitoQ.” Using this orally bioavailable, over-the-counter antioxidant, they show that the endothelium-dependent vasodilation of carotid arteries is protected in mice treated with a single high dose of doxorubicin. Noting a drop in the levels of vascular endothelial growth factor A (VEGF-A), the investigators advance the hypothesis that doxorubicin disruption of endothelial VEGF could be central to the effects of doxorubicin on arterial function.

Preclinical experiments and clinical studies looking to understand and prevent anthracycline-associated cardiovascular dysfunction abound, and it is worth considering how the current study jives with the rest of this literature. Anthracyclines are used clinically in multiple distinct dosing schedules, and the significance of preclinical studies should be considered in this context. In the current experimental protocol, Clayton et al. (1) use a single high-dose exposure, similar to induction chemotherapy in the treatment of some hematologic malignancies, and different from the multiple cycles of anthracycline-based chemotherapy used in solid tumors such as breast cancer. In this context, it is notable that childhood survivors of hematologic malignancies treated with anthracycline-based chemotherapy do show signs of persistent impaired vascular endothelial function (4). In contrast, these same changes do not persist in adult breast cancer survivors who received a series of lower-dose exposure to anthracyclines (5). This clinical literature suggests that the findings by Clayton et al. (1) may be most translatable to a subset of anthracycline-treated patients.

With regards to mechanistic insights suggesting disrupted VEGF-A as a mediator of the vascular

\*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

From the Maine Medical Center, Tufts University School of Medicine, Portland, Maine. The author has reported that he has no relationships relevant to the contents of this paper to disclose.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* [author instructions page](#).

dysfunction, some clinical data does not support that hypothesis. The effect of anthracyclines on circulating VEGF-A and other cardiovascular growth factors has been examined in samples collected from children undergoing anthracycline-based chemotherapy. Plasma levels of VEGF-A increased after anthracycline treatment in contrast to what was seen in this mouse studies of Clayton et al. (1,6). In contrast, the cardiovascular growth factors neuregulin (NRG) and cardiotrophin-1 decreased after anthracycline treatment in these same children (6). The decrease in NRG after anthracyclines has also been observed in adults undergoing anthracycline-based chemotherapy, which is interpretable as a sign of vascular endothelial cell injury (7). Endothelial cell-derived NRG acts through the ERBB receptor tyrosine kinase family to regulate the growth and survival of cardiac myocytes, and protects from anthracycline cardiac cytotoxicity (8,9). Given the interaction between VEGF-A and NRG in regulating the adaptation of the cardiovascular system to stress and the clinical data showing anthracycline-associated decline in plasma NRG, further work should be considered (10).

Perhaps the trickiest part of interpreting the work by Clayton et al. (1) is when answering questions from

patients anticipating anthracycline-based treatment. MitoQ and other coenzyme Q10 preparations are available over the counter, and coenzyme Q10 supplementation has been studied not only as a way to limit injury to the cardiovascular system, but also kidney and reproductive organs (11,12). These promising preclinical results may lead people to self-medicate during their cancer treatment. As Clayton et al. (1) acknowledge, that would be a bad idea. They acknowledge that the National Cancer Institute guidelines specifically warn against taking antioxidants concurrent with chemotherapy. In fact coenzyme Q10 was among a group of dietary supplements that was associated with worse outcomes in people being treated for breast cancer (13). So, unless a definitive clinical study is conducted showing a beneficial effect of MitoQ in this clinical setting, it seems the best advice we can currently give is to leave the MitoQ on the shelf.

---

**ADDRESS FOR CORRESPONDENCE:** Dr. Douglas B. Sawyer, Maine Medical Center, Tufts University School of Medicine, 22 Bramhall Street, Portland, Maine 04102. E-mail: [dsawyer@mmc.org](mailto:dsawyer@mmc.org). Twitter: [@MaineHealth](https://twitter.com/MaineHealth), [@MaineMed](https://twitter.com/MaineMed).

## REFERENCES

1. Clayton ZS, Brunt VE, Hutton DA, et al. Doxorubicin-induced oxidative stress and endothelial dysfunction in conduit arteries is prevented by mitochondrial-specific antioxidant treatment. *2020*;2:475-88.
2. Folkers K, Liu M, Watanabe T, Porter TH. Inhibition by Adriamycin of the mitochondrial biosynthesis of coenzyme Q10 and implication for the cardiotoxicity of Adriamycin in cancer patients. *Biochem Biophys Res Comm* 1977;77:1536-42.
3. Conklin KA. Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. *Integ Cancer Ther* 2005;4:110-30.
4. Jenei Z, Bárdi E, Magyar MT, Horváth Á, Paragh G, Kiss C. Anthracycline causes impaired vascular endothelial function and aortic stiffness in long term survivors of childhood cancer. *Pathol Oncol Res* 2013;19:375-83.
5. Koelwyn GJ, Lewis NC, Ellard SL, et al. Ventricular-arterial coupling in breast cancer patients after treatment with anthracycline-containing adjuvant chemotherapy. *Oncologist* 2016;21:141.
6. Lipshultz SE, Scully RE, Smith HM, et al. Serum cardiovascular growth factors during doxorubicin chemotherapy in children with leukemia. In Proceedings of the 5th World Congress of Paediatric Cardiology and Cardiac Surgery (PCCS'09). 2009; 133. Presented Queensland, Australia, June 21, 2009.
7. Geisberg CA, Abdallah WM, da Silva M, et al. Circulating neuregulin during the transition from stage a to stage b/c heart failure in a breast cancer cohort. *J Card Fail* 2013;19:10-5.
8. Kuramochi Y, Cote GM, Guo X, et al. Cardiac endothelial cells regulate ROS-induced cardiomyocyte apoptosis through neuregulin-1beta/erbB4 signaling. *J Biol Chem* 2004;279:51141-7.
9. Fukazawa R, Miller TA, Kuramochi Y, et al. Neuregulin-1 protects ventricular myocytes from anthracycline-induced apoptosis via erbB4-dependent activation of PI3-kinase/Akt. *J Mol Cell Cardiol* 2003;35:1473-9.
10. Kivelä R, Hemanthakumar KA, Vaparanta K, et al. Endothelial cells regulate physiological cardiomyocyte growth via VEGFR2-mediated paracrine signaling. *Circulation* 2019;139:2570-84.
11. El-Sheikh AA, Morsy MA, Mahmoud MM, Rifaai RA. Protective mechanisms of coenzyme-Q10 may involve up-regulation of testicular P-glycoprotein in doxorubicin-induced toxicity. *Environ Toxicol Pharmacol* 2014;37:772-81.
12. Aly NH. Reno-protective efficiency of coenzyme Q10 on Adriamycin-induced nephrotoxicity in rats. *J App Sci Res* 2012;8:589-97.
13. Ambrosone CB, Zirpoli GR, Hutson AD, et al. Dietary supplement use during chemotherapy and survival outcomes of patients with breast cancer enrolled in a cooperative group clinical trial (SWOG S0221). *J Clin Oncol* 2020;38:804-14.

---

**KEY WORDS** antioxidants, coenzyme Q10, doxorubicin, endothelial dysfunction, endothelium, mitochondrial function, oxidative stress, vascular endothelial growth factor