

Cardiac Toxicity and Anthracyclines: Mechanism, Interventions, and the Trouble With Troponin

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

As cancer survivorship increases, clinicians need to become educated regarding the long-term effect of cancer treatments. Cancer therapeutics-related cardiac dysfunction (CTRCD) is one such sequela that contributes to significant morbidity and mortality. Unfortunately, screening and management practices regarding CTRCD are inconsistent within guidelines and practice. This review will first look at anthracycline-related cardiac dysfunction occurrence and pathophysiology. Current guidelines for CTRCD screening will be discussed, including the use of 2D echocardiograms along with newer technology such as 3D echocardiography and global systolic longitudinal myocardial strain (GLS) measurements. Biomarkers like serum troponin demonstrate promise as an early indicator of cardiomyocyte injury and a potential means of risk stratification; however, guidelines vary regarding how best to incorporate elevated serum troponin levels into management plans. Growing evidence indicates the clinical need for early detection of CTRCD in order to initiate preventative pharmacologic management and improve patient outcomes.

Cancer survivorship has increased partly due to the plethora of new cancer treatments. Half of adults diagnosed with cancer today will survive at least 10 years; in childhood cancer survivors, the survivorship number is closer to 75% (Henriksen, 2018). An estimated 14.5 million people in the United States are currently living with a history of cancer (Jain, Russell, Schwartz, Panjath, & Aronow, 2017). As the number of cancer survivors increases, clinicians need to become educated regarding the long-term effects of cancer treatments, including cardiac toxicity. Cancer therapeutics-related cardiac dysfunction (CTRCD) contributes to significant morbidity and mortality (Singh, Thakur, & Tang, 2015). The problem has become so critical that an entire specialty, cardio-oncology, has emerged

to combat the issue. General estimates of CTRCD include 5% to 20% for asymptomatic decrease in left ventricular ejection fraction (LVEF) and 1% to 5% for clinically overt heart failure (Singh et al., 2015). However, the incidence of cardiac toxicity varies depending on the agent (Singh et al., 2015). In patients who develop heart failure secondary to cancer therapy, the mortality rate can be as high as 60% in 2 years (Felker et al., 2000).

ANTHRACYCLINE CARDIAC TOXICITY: EVENT RATES AND PATHOPHYSIOLOGY

Anthracyclines are the most studied drug class in relation to cardiac dysfunction occurrence and pathophysiology in oncology patients. Anthracycline chemotherapy agents are a class of antibiotics that are isolated from soil microbes and include doxorubicin, daunorubicin, epirubicin, and idarubicin. They are a well-established, highly effective class of agents used in the treatment of a variety of adult and pediatric cancers, including breast and solid organ tumors, leukemias, and lymphomas (Singh et al., 2015).

Anthracycline administration has been associated with dose-related cardiomyocyte injury (Henriksen, 2018). Anthracycline-induced cardiomyopathy exists on a spectrum that can range from development of heart failure with clinical signs and symptoms to asymptomatic decline in LVEF (Henriksen, 2018). Because CTRCD can manifest in various forms, it is particularly hard to define. As there is no single universally accepted definition, it is challenging to compare results across trials (Levis, Brinkley & Shapiro, 2017). A retrospective analysis of three studies examining congestive heart failure in patients treated with doxorubicin found the estimated cumulative percentage of patients with doxorubicin-related heart failure to be 5% of patients given a cumulative dose of 400 mg/m², 26% of patients at 550 mg/m², and 48% at 700 mg/m² (Swain, Whaley & Ewer, 2003).

Currently, the mechanism of anthracycline cardiotoxicity is thought to be related to anthracycline inhibition of topoisomerase (Top), resulting in an increase in DNA breaks preventing DNA and RNA synthesis (Henriksen, 2018). In cancer cells, anthracyclines inhibit Top 2 α , leading to cancer cell death; however, anthracyclines can also inhibit Top 2 β , an enzyme found in quiescent non-

proliferating cells such as cardiomyocytes (Henriksen, 2018). Inhibition causes double-stranded DNA breaks that can mediate the apoptotic cell death pathway and also interfere with mitochondrial biogenesis (Henriksen, 2018). Anthracyclines also contain an anthraquinone ring that has a role in redox cycling resulting in formation of hydrogen peroxide and reactive oxygen species causing potential damage to the cardiomyocyte (Zhang et al., 2012).

Anthracyclines are not the only chemotherapy agent associated with left ventricular dysfunction. Some of the other chemotherapy agents implicated in a reduction of LVEF include monoclonal antibodies, sunitinib (Sutent), sorafenib (Nexavar), and lapatinib (Tykerb; Singh et al., 2015).

CARDIOTOXICITY SCREENING: CURRENT TECHNIQUES

The current practice of cardiac surveillance includes a 2D echocardiogram to evaluate LVEF prior to initiating therapy and additional echocardiograms throughout treatment to monitor for the development of cardiotoxicity (Christenson, James, Agrawal, & Park, 2015). The echocardiograms look for a reduction in left ventricular function without signs or symptoms of heart failure that correlates with the definition of stage B heart failure (Thavendiranathan et al., 2014). The specific timing of subsequent echocardiograms depends on the type of chemotherapy, presence of risk factors, and the dose (Singh et al., 2015). With anthracyclines, current protocols guided by expert consensus typically recommend quantifying LVEF both prior to initiating treatment and following completion of chemotherapy with additional on-therapy measurements if patients are receiving cumulative doses over 200 mg/m² of doxorubicin (Henriksen, 2018). In individuals treated with an anthracycline, a low baseline LVEF (50%–55%) and an asymptomatic decrease in LVEF increase the risk of future heart failure (Levis et al., 2017).

One major problem with the use of serial cardiac echocardiograms as a screening tool for CTRCD is that reduced LVEF is often a late finding and is associated with worse outcomes (Thavendiranathan et al., 2014). There is a failure to recover systolic function in up to 58% of patients

despite intervention (Thavendiranathan et al., 2014). A successful cardiovascular surveillance strategy would also detect myocardial damage early enough to intervene effectively, but 2D echocardiography has poor sensitivity in detecting subclinical myocardial injury (Levis et al., 2017). Cardiac MRI is regarded as the gold standard for evaluating systolic and diastolic cardiac function; however, it is expensive and has limited availability (Levis et al., 2017). Real-time 3D echocardiography appears to have advantages over 2D echocardiography but is also associated with increased cost and limited availability, and requires specially trained technicians (Levis et al., 2017).

Global systolic longitudinal myocardial strain (GLS) is a newer echocardiographic technology that shows promise for earlier myocardial injury recognition (Thavendiranathan et al., 2014). Strain is a dimensionless index that reflects the total deformation of the ventricular myocardium given as a percentage of its initial length (Thavendiranathan et al., 2014). Reductions in measures of myocardial deformation are a sign of subclinical myocardial changes (Thavendiranathan et al., 2014).

A meta-analysis of three studies with 1,504 subjects found that myocardial deformation preceded significant change in LVEF (Thavendiranathan et al., 2014). The most useful parameter for prediction of cardiotoxicity development was a 10% to 15% early reduction in GLS found using the echocardiographic technique of speckle tracking echocardiography (Thavendiranathan et al., 2014).

However, the use of GLS measurements could potentially be limited in that the diagnostic technique can be noisy and significant expertise is required for interpretation (Thavendiranathan et al., 2014). The utility of a left ventricular strain measurement may be limited in patients with obesity, valvular heart disease, left ventricle hypertrophy, coronary artery disease, and old age (Jain et al., 2017). These limitations are particularly relevant as the pathologies involved (i.e., obesity, old age) are widespread, potentially negating the benefit of the test.

With all of the tools at a clinician's disposal, Cautela and colleagues (2016) emphasize the need for a standardized baseline cardiovascular evaluation as well as a standardized cardiovas-

cular monitoring protocol during and after cancer treatment.

TROPONIN: ROLE IN SURVEILLANCE

There has been increased interest in discovering markers of early myocardial changes outside the expensive and specialized technology realm that could potentially predict the development of reduced LVEF or progression to heart failure so that preventive strategies can be implemented (Thavendiranathan et al., 2014). One proposed screening method is the use of biomarkers such as troponin or BNP (B-type natriuretic peptide). BNP is well established as a biomarker in decompensated heart failure and may have a role in the surveillance of cancer survivors, especially if the presenting symptom is dyspnea (Henriksen, 2018).

Troponin is a three-unit complex consisting of troponins T, I, and C, which is located along with tropomyosin on the actin filament and is required for calcium-mediated cardiac and skeletal muscle contraction (Chaudry, Banchs, & Chavez-MacGregor, 2016). Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have shown promise as potential early indicators of cardiac muscle injury (Henriksen, 2018). Cardiac troponin I (cTnI) is not expressed in skeletal muscles or other tissues and is uniformly distributed between atria and ventricles, making it cardiac specific (Chaudry et al., 2016). Cardiac troponin T (cTnT) is tricky in that it is also expressed in diseased skeletal muscle; however, new assays have eliminated false-positive elevation from skeletal muscle (Chaudry et al., 2016).

High-sensitivity assays exist for both cTnI and cTnT. Cardinale and colleagues (2004) stratified 703 patients receiving anthracycline high-dose chemotherapy according to whether they exhibited increased cTnI concentrations (which was defined as > 80 ng/L). The study measured cTnI soon after chemotherapy (early TnI) and 1 month later (late TnI; Cardinale et al., 2004). All patients had an LVEF that was normal at baseline (Cardinale et al., 2004). Cardinale and colleagues (2004) found that in the 70% (n = 495) of patients with no elevation (meaning both early TnI and late TnI were < 80 ng/L), the cumulative cardiac events rate was 1%. However, the group that demonstrated elevations in both early TnI and late TnI (n =

63) demonstrated a cumulative cardiac events rate of 84% (Cardinale et al., 2004). Cardiac events included sudden and cardiac death, pulmonary edema, heart failure, asymptomatic left ventricular dysfunction, life-threatening arrhythmias, and conduction disturbances requiring pacemakers (Cardinale et al., 2004).

Guidelines for Troponin Screening

The research and clinical guidelines regarding troponin as a screening method for CTRCD are neither consistent nor developed. Some of the challenges of the current available data are the timing of the troponin laboratory draw in relation to chemotherapy, the definition of the upper limit of normal, the difference in laboratory assays, and the appropriate strategy if given an abnormal result (Zamorano et al., 2016). With these challenges in mind, we will focus on the guidelines from the European Society for Medical Oncology (ESMO), the Canadian Cardiovascular Society (CCS), the European Society of Cardiology (ESC), and a joint effort between the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).

The 2012 ESMO guidelines support the use of troponin for detecting drug-induced cardiotoxicity in its earliest phase, long before a reduction in LVEF occurs (Curigliano et al., 2012). The European Society for Medical Oncology's guidelines support evaluating troponin levels during high-dose chemotherapy, as this can help identify patients that are at risk for cardiac dysfunction, providing clinicians an opportunity to intervene with preventative measures (Curigliano et al., 2012). Troponin levels could also provide a means to stratify the risk of future cardiac events. However, the ESMO guidelines do not articulate how risk is to be stratified, nor do they specify a range of troponin that is considered low risk, medium risk, or high risk. The European Society for Medical Oncology states there is a strong case to incorporate troponin I concentrations to assess cardiac baseline but points out that routine monitoring has not yet been proven useful (Curigliano et al., 2012). For ongoing cardiac monitoring, ESMO recommends periodic (defined as after each cycle of treatment) measurements of troponin I and 2D echocardiograms in order to identify patients who

may require further cardiac assessment (Curigliano et al., 2012).

The 2016 CCS guidelines suggest the serial use of cardiac biomarkers for early detection of cardiotoxicity, but CCS cites it as a weak recommendation (Virani et al., 2016). The Canadian Cardiovascular Society does not define "serial" in terms of frequency or timing. It states that further prospective studies are warranted to evaluate the use of cardiac biomarkers to "identify a subset of patients at highest risk" (Virani et al., 2016). It also acknowledges ESMO's recommendation for serial echocardiograms and troponin levels but points out that "the feasibility and cost effectiveness of this multimodality approach is not defined and has not yet been evaluated in the cancer community at large" (Virani et al., 2016).

The American Society of Echocardiography's 2014 recommendations emphasize an integrated approach to CTRCD surveillance, combining echocardiographic data and biomarkers (Plana et al., 2014). The American Society of Echocardiography recommends a baseline cardiac assessment for every patient scheduled to receive a potentially cardiotoxic agent, while acknowledging that this is often not possible (Plana et al., 2014). Ideally, this baseline assessment includes a troponin level, but the guidelines do not stipulate a specific assay (Plana et al., 2014). If anything is abnormal, a cardiology consult should be considered with an active discussion on the risk/benefit ratio of the treatment (Plana et al., 2014). Regarding cardiac surveillance, ASE recommends patients be "longitudinally followed for evidence of CTRCD or subclinical LV dysfunction (defined as abnormal GLS or elevated troponin)" (Plana et al., 2014). cTnI levels are measured before and/or 24 hours after each chemotherapy cycle (Plana et al., 2014). Plana and colleagues (2014) also discuss the added prognostic benefit of looking at troponin levels in conjunction with GLS. If both are abnormal, the specificity for CTRCD increases from 73% to 93%; if both are negative, the negative predictive value decreases to 91% (Plana et al., 2014).

The European Society of Cardiology 2016 guidelines also emphasize the importance of identifying patients at increased risk for cardiotoxicity via a risk assessment that includes clinical history, exam, and baseline measures of cardiac func-

tion (Zamorano et al., 2016). The European Society of Cardiology states that cardiac biomarkers may also be considered (Zamorano et al., 2016). For cardiac surveillance, ESC does acknowledge that an elevation in troponin from baseline “may identify those who develop cardiac dysfunction with a poor prognosis,” particularly when the elevation persists (Zamorano et al., 2016). However, ESC points out the major limitations of cardiac biomarkers, including insufficient evidence to establish the significance of subtle rises, variations within different assays, and the fact that the role of routine surveillance is not clearly established (Zamorano et al., 2016).

The above guidelines generally agree that a troponin level is useful information to obtain for the initial cardiac assessment; however, guidelines vary as to how to incorporate troponin serum levels into ongoing cardiotoxicity surveillance. Several guidelines mention the relevance of rising troponins and their implications in terms of risk stratification; however, there is no clear consensus as to what constitutes a “rising troponin,” and there are no data that clearly establish the benefit of routine troponin level surveillance. This confusion is evident in clinical practice. In France, Jovenaux and colleagues (2017) surveyed 303 oncologists and found that only 30% were aware of using biomarkers such as troponin for early screening of left ventricular dysfunction. Only 7% of oncologists surveyed used troponin serum level assessment when using anthracyclines (Jovenaux et al., 2017).

CURRENT MANAGEMENT OF CANCER THERAPEUTICS-RELATED CARDIAC DYSFUNCTION

We have discussed the various screening methods for CTRCD with a focus on the role of troponin serum assays. But as clinicians, when we discuss screening for a given pathology, it is imperative to consider the current treatments or interventions that exist for said pathology. Current treatment for CTRCD mimics heart failure therapies in that the primary agents in play include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and beta blockers (Jain et al., 2017). Any ACE inhibitor or ARB can be considered, but only the beta blockers carvedilol

and nebivolol have been proven effective in treating anthracycline cardiotoxicity (Jain et al., 2017). Other treatments include dexrazoxane, an iron chelator that has been shown to reduce the cardiotoxicity of anthracyclines; however, its use has been limited by the adverse effects of myelosuppression (Jain et al., 2017).

Statins have been studied for their antioxidative, anti-inflammatory, and pleiotropic effects (Curigliano et al., 2016). Animal models have demonstrated a blunting of anthracycline-related toxicity with pretreatment using statins (Curigliano et al., 2016). One retrospective study looked at women who were treated with anthracyclines: 67 women were on uninterrupted statin therapy concurrently with the anthracycline, while the 134 controls were not on any statin. Cox regression analysis showed a significantly lower hazard ratio (0.3) in the statin group ($p = .03$; Seicean, Seicean, Plana, Budd & Marwick, 2012). Statins appear promising but more prospective studies need to be conducted.

When should a patient start on an ACE inhibitor, ARB, or beta blocker? Some studies indicate that earlier initiation of ACE inhibitors/ARBs and beta blockers lead to better outcomes. In a study of 226 patients who developed cardiotoxicity post anthracycline use, 11% exhibited full recovery of LVEF with treatment with enalapril or the combination of enalapril plus beta blocker (Cardinale et al., 2015). In another study of 201 patients, when combined enalapril and carvedilol were initiated early (within 6 months of anthracycline therapy), there was greater LVEF recovery (a return to baseline in 42% of patients; Cardinale et al., 2010). Henriksen (2018) notes that although the studies are purely observational (and lack a control group), they illustrate the potential benefit of early treatment and as an extension the benefit of a screening methodology that could detect the pathology at an earlier stage.

CONCLUSION

As cancer survivorship increases, clinicians need to become more proactive and aggressive in the management of CTRCD. 2D echocardiograms remain the screening standard for CTRCD, despite limitations of the technology. Screening guidelines are beginning to incorporate other

techniques that are more effective in detecting subclinical damage, including measures of GLS, although adoption may be slow due to high cost and limited availability. Serum biomarkers, such as troponin serum levels, are being explored as indicators of cardiac dysfunction or identifiers of individuals at risk of a cardiac event. Troponin serum levels show real promise as a diagnostic and risk stratification tool, especially in cases in which the troponin level remains persistently elevated. In patients who previously received anthracycline therapy, it appears reasonable for providers to include, at minimum, a baseline troponin level as part of the cardiac assessment.

Unfortunately, guidelines are inconsistent as to the timing, role, and significance of troponin measurements. If they are found to be elevated, should troponin levels change the treatment plan? Providers could potentially opt to stop or switch the anthracycline treatment all together or potentially start a preventative medication (ACE inhibitor, ARB, or beta blocker). It appears that in terms of the detection of and treatment initiation for CTRCD, the earlier the better; however, these actions could be seen as premature based on current evidence and guidelines to avoid overtreatment with unnecessary drugs. Robust research is needed to successfully detect CTRCD earlier and to agree upon treatment interventions to improve patient outcomes. ●

Disclosure

Ms. Thompson has no conflicts of interest to disclose.

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