volume in patients receiving aromatase inhibitors is due to
the discontinuation of tamoxifen treatment and not a direct
effect of aromatase inhibitors. As we mentioned in our
article [1], future clinical trials looking at the endometrial
safety of endocrine treatments, particularly those trials
involving sequential treatments with selective estrogen
receptor modulators and aromatase inhibitors, should also
take into account the potential effect on the uterus of a
wash-out period after tamoxifen treatment. Only then can
we determine whether tamoxifen-induced changes would
eventually resolve over time or whether aromatase inhibitors
can offer a protective effect on the endometrium of patients
treated with tamoxifen. While there are data on how endo-
metrial thickness decreases over time following discontinu-
tation of tamoxifen treatment [2], a direct comparison with
the decrease achieved in patients receiving aromatase inhibi-
tors is not available. Likewise, whether a difference in ute-
rine effects between steroidal and non-steroidal aromatase
inhibitors exists or whether there is a difference between
the three agents is not known. Furthermore, the potential of
aromatase inhibitors to reverse tamoxifen-induced uterine
changes should be confirmed through randomized clinical
trials. Recently, the Intergroup Exemestane Study presented
data similar to ours, showing the decrease in endometrial
thickness and uterine volume in women receiving exemes-
tane compared with tamoxifen [3].

The second issue raised by Cohen is whether the polyps
visualized by transvaginal sonography in the present study
were real endometrial polyps and not subendometrial fibroids.
In our institution, color Doppler imaging is routinely per-
formed to confirm the presence of a polyp. In a prospective
observational study on 3099 consecutive patients referred for
the assessment of the endometrium and myometrium, 182
polyps were detected and 139 of them had a clear feeding
vessel. A distinct vascular pedicle from the myometrium
reaching at least the middle of the endometrium (called the
‘pedicle artery sign’) was related to the presence of a polyp in
81% of the patients, or to any focal lesion in 94.2% of cases
[4]. We also reported that this sign was observed in 32 of 687
patients without an endometrial polyp. However, 22 of the 32
patients with false-positive results had other intracavitary
pathology: submucous fibroids (7%), hyperplasia (2.9%),
endometrial cancer (1.8%) and persistent trophoblastic tissue
(1.2%). Only in 5.8% of the patients with a positive test was
the cavity normal. These findings were very similar for 310
tamoxifen-treated patients, where the ‘pedicle artery test’ had
a sensitivity for detecting polyps of 89%, specificity of 86%,
positive predictive value of 85% and negative predictive value
of 89%. Overall accuracy was 87% [5]. In addition to the pre-


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Is cardiac troponin T serum level
an accurate surrogate for acute
doxorubicin-related myocardial
injury?

Since anthracyclines are still among the most frequently used
antineoplastic drugs, early detection and/or prediction of
anthracycline-induced cardiotoxicity is urgently needed. Serum
levels of cardiac troponin T (cTnT) are increasingly
becoming recognized as potential biochemical markers of
even subclinical myocardial injury. In a recent paper,
Lipschultz et al. [1] affirmed that ‘the serum level of cardiac
troponin T is an accurate surrogate for acute myocardial injury
in children, specifically that related to doxorubicin’. The same
authors previously showed that low-level elevations of cardiac
troponin T induced by doxorubicin were associated with
histological evidence of myocardial injury [2], and that
dexrazoxane-treated rats had less frequent elevations in car-
diac troponin T and less severe cardiac injury on histological
analysis and were in better health than rats that did not receive
dexrazoxane [3].
Despite these findings, there is still little information about the exact mechanisms responsible for the cTnT release, especially with regard to the gradual development of myocardial injury, and the role of cTnT in diagnosis and monitoring of cardiac damage remains controversial. Moreover, the lack of evaluation of diastolic heart function represents a negative point of design of the study by Lipshultz and colleagues. Therefore the question immediately arises as to whether the diastolic heart function may have a non-negligible power for prediction of chronic/late cardiotoxicity of anthracyclines. As a consequence, the identification of a reliable serum indicator of early diastolic dysfunction in cardiomyocytes after doxorubicin treatment could be advisable.

Doxorubicin cardiomyopathy is typically associated with myofibrillar deterioration and intracellular calcium overload, which may trigger indiscriminate activation of calcium-dependent proteases resulting in degradation of key myofibrillar proteins. In animal models, oxidative damage to the sarcoplasmic reticulum (SR) and activation of the sarcolemmal L-type calcium channels or the SR ryanodine receptors would result in calcium accumulation in the cytosol, which alone may be sufficient for activation of calpains. In adult rat ventricular myocytes, calpain-mediated proteolysis of the elastic domain of titin, whose extensible segment underlies the passive and restoring forces of the cardiomyocyte and helps to maximize myocardial efficiency, can predictably lead to impaired diastolic or systolic function, both of which can occur acutely after doxorubicin treatment [4].

Because dexrazoxane reduces free-radical injury, the findings by Lipshultz et al. [1] suggest that doxorubicin-associated myocardial injury may be related, at least in part, to oxidative damage. The attenuating effect of dexrazoxane on doxorubicin-induced cardiotoxicity may be attributable to intracellular conversion to its active form (ADR-925), which binds free iron or removes it from the doxorubicin–iron complex, thus preventing the formation of oxygen radicals. However, chronic cardiomyopathy develops after summation and mutual feedback of multifactorial processes. Whether, and how, these processes contribute to inducing cardiotoxicity in patients is controversial, and it is not clear how precisely iron and reactive species of the oxygen intervene in these multiple settings [5].

Thus, the exclusive use of cTnT as an indicator of subclinical doxorubicin-related myocardial injury in children with cancer cannot completely reflect the acute contractile dysfunction caused by doxorubicin. On the contrary, since the stretch-sensitization response is essential to the regulation of heart contractility, calpain-mediated proteolysis of the elastic domain of titin may have acute physiological consequences, predisposing cardiomyocytes to diastolic dysfunction, myofilament instability and necrosis [4]. Unfortunately, this finding has been demonstrated only in a rat myocyte model. Reliable serum markers capable of early detection of the disassembly of the myofilament complex during the normal sarcomere turnover are urgently needed, and may offer a novel diagnostic tool for the acute contractile dysfunction associated with doxorubicin-induced myocardial calcium overload and oxidative stress.

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