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Natriuretic peptide and cardiac troponin levels in doxorubicin-induced cardiotoxicity

To the Editor,

We read with a great interest the paper by Argun et al. (1) entitled "Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats" published in the Anatolian Journal of Cardiology 2015 as Epub ahead of print. The authors aimed to investigate the effectivity of metformin in doxorubicin-induced cardiotoxicity using cardiac markers in blood and histopathological examination in the rat model. They concluded that metformin improved the left ventricular function, histopathologic change, and cardiomyocyte apoptosis. We congratulate the authors for this valuable investigation, and we have a few comments.

Doxorubicin (DXR) is a very effective and commonly used chemotherapeutic drug for the treatment of different types of cancers. It blocks cell division and growth by interacting DNA and RNA formation. However, it can cause a life-threatening heart damage, resulting in left ventricular dysfunction, thus limiting its usage (2).

Both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are useful predictors of decreased left ventricular function in patients treated with DXR. ANP secretion from atria is triggered by atrial dilatation due to cardiac or noncardiac reasons. BNP is produced in the ventricle and is more specific for heart failure than ANP (1–3). Koh et al. (3) reported that plasma BNP levels significantly increased from 6 to 12 weeks in the doxorubicin-induced cardiotoxicity. In the study by Argun et al. (1), there was no statistical difference among groups in terms of ANP or BNP. This may be due to the design of the study, which is relatively short for the occurrence of chronic heart failure because of DXR.

Cardiac troponin (TnT) is a very specific and highly sensitive marker for myocardial damage and commonly used in clinical practice. Similar to BNP, TnT has been reported as an independent predictor of cardiac mortality in heart failure (2–4). In the study by Argun et al. (1), it would have been very helpful to measure TnT levels in terms of myocardial injury due to DXR. Thus, one could make an interpretation that TnT levels had increased in the early stage in the DXR-induced cardiotoxicity, but no change were observed in the BNP levels, which is very crucial for the early detection of DXR-induced cardiotoxicity before irreversible damage.

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Author`s Reply

To the Editor,

Many thanks to the authors for their important comments to our paper entitled "Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats" published in the Anatolian Journal of Cardiology 2015 as Epub ahead of print (1). It is of great importance to detect cardiotoxicity as early as possible in patients receiving cardiotoxic chemotherapy. This would make it possible to minimize cardiotoxicity-associated mortality and morbidity.

The role of cardiac biomarkers such as cardiac troponins and natriuretic peptides in the prediction of chemotherapy-induced cardiotoxicity has been investigated in animal models and clinical studies. These studies have focused on the early detection of cardiotoxicity and/or the relative sensitivities of the available biomarkers for the prediction of cardiotoxicity.

As you indicated, our study could have achieved more significant results if troponins had also been studied in conjunction with brain natriuretic peptide (BNP). Although some studies have not reported significant chemotherapy-induced elevations in tro-

ponin levels, many others have reported that troponin levels are elevated during chemotherapy, a phenomenon that was correlated to the extent of the impairment of left ventricular systolic performance. Some other similar studies have provided evidence for a correlation between higher troponin levels and low left ventricular ejection fraction. Cardinale et al. (2) determined troponin I levels before, during, immediately after, and one month after chemotherapy in 703 cancer patients. The percentage of patients with persistently negative troponin I levels was 70%, that of patients with troponin elevation only in early evaluation was 21%, and that of patients with troponin elevation in both early and late evaluations was 9%. During a 3.5-year follow-up, adverse cardiac events were reported in 1%, 37%, and 84% of the subjects, respectively. These results suggest that troponin I can be used to determine the risk of cardiotoxicity both during and after chemotherapy.

Brain natriuretic peptide has a prognostic value in heart failure. Many studies scrutinizing chemotherapy-induced cardiotoxicity have provided evidence of increased BNP levels in subjects with impaired myocardial function. Sandri et al. (3) examined N-terminal proBNP levels before, at the onset of, and 72 h after chemotherapy in 52 cancer patients. They reported a strong correlation between persistent N-terminal proBNP elevation at an early period after chemotherapy and cardiac dysfunction.

There are a limited number of studies examining the role of BNP and troponins combined. In an experimental rat model where they administered intravenous 2 mg/kg doxorubicin for 8 weeks, Koh et al. (4) reported that the increase in BNP and troponin levels and the reduction in fractional shortening (FS%) were significant through 6^{th} to 12^{th} weeks, with the reduction in FS% being significantly negatively correlated to increases in BNP and troponin T levels. They also reported that the increase in troponin T level preceded that in BNP level and the decrease in FS%. Sawaya et al. (5), in a study involving 43 breast cancer patients receiving anthracycline and trastuzumab, found that troponin I and longitudinal strain were predictive of cardiotoxicity, whereas ejection fraction and N-terminal proBNP failed to predict cardiotoxicity.

In conclusion, there is some evidence that elevated troponin levels and persistent BNP elevation during chemotherapy are the risk factors for cardiotoxicity. We are of the opinion that whether an increase in troponin I levels precedes the one in BNP levels should be further tested by experimental and clinical studies.

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Late huge thrombus formation after percutaneous closure of an atrial septal defect with an Amplatzer septal occluder: Implications of Kounis syndrome

To the Editor,

Common causes of thrombus formation following implantation of cardiac devices include incorrect device placement, device size, device instability, hypersensitivity to device components, foreign body reaction, anticoagulation, and antiplatelet therapy monitoring. In the very important paper entitled "Huge thrombus formation 1 year after percutaneous closure of an atrial septal defect with an Amplatzer septal occluder" published in the Anatolian Journal of Cardiology (1), a 17-year-old boy who was diagnosed with an atria septal defect (ASD) developed a huge mobile thrombus one year after an Amplatzer septal occluder device implantation. The thrombus and device were surgically removed, and examination of the thrombus revealed the presence of peripheral blood elements and fibrin but not acute or granulomatous inflammation. Although the authors did not describe any symptomatology or electrocardiographic findings, it is presumed that the peripheral blood elements in the removed thrombus were red cells, lymphocytes, monocytes, and multinucleated leukocytes including neutrophils, basophils and eosinophils.

This case raises important questions concerning the etiology of thrombus formation.

The Amplatzer septal occluder contains nitinol, an alloy composed of 45% titanium and 55% nickel. These two metals can release metal ions while they are embedded in the atrial septal defect and are directly in touch with the blood stream. Such an-