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.

Mustafa Argun, Kazım Üzüm[1], Ali Baykan[1], Nazmi Narin[1]
Department of Pediatric Cardiology, Necip Fazıl City Hospital, Kahramanmaraş-*Turkey*
[1]Department of Pediatric Cardiology, Faculty of Medicine, Erciyes University, Kayseri-*Turkey*

References

1. Argun M, Üzüm K, Sönmez MF, Özyurt A, Karabulut D, Soyersarıca Z, et al. Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats. Anatol J Cardiol 2015 Apr 30. Epub ahead of print.
2. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotheraphy. Circulation 2004; 109: 2749-54.
3. Sandri MT, Salvatici M, Cardinale D, Zorzino L, Passerini R, Lentati P, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotheraphy: a marker predictive of cardiac dysfunction? Clin Chem 2005; 51: 1405-10.
4. Koh E, Nakamura T, Takahashi H. Troponin T and brain natriuretic peptide as predictors for adriamycin-induced cardiomyopathy in rats. Circ J 2004; 68: 163-7.
5. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotheraphy-treated patients. Am J Cardiol 2011; 107: 1375-80.

Address for Correspondence: Dr. Mustafa Argun
Erciyes Üniversitesi Tıp Fakültesi, Pediyatrik Kardiyoloji Bölümü
38039 Kayseri-*Türkiye*
Phone: +90 352 207 66 66 Fax: +90 352 437 58 25
E-mail: dr.margun@hotmail.com