

# The cardioprotective role of trimetazidine on cisplatin-induced cardiotoxicity

To the Editor,

We have read the article by Zhao (1) entitled "Protective effects of trimetazidine and coenzyme Q10 on cisplatin-induced cardiotoxicity by alleviating oxidative stress and mitochondrial dysfunction" with great interest. The authors reported that trimetazidine and coenzyme Q10 showed protective effects against cisplatin-induced cardiotoxicity by reducing oxidative stress. First, we wish to ask the authors how they have rationalized the concentrations of trimetazidine (200 µM) and coenzyme Q10 (200 mg/L) they used in the ventricular myocytes? We would like to emphasize some important points about this well-written study.

Intracellular calcium plays a key role in cellular homeostasis. One of the most important mechanisms underlying chemotherapy-induced cardiotoxicity is increased calcium (Ca<sup>2+</sup>) levels in cardiomyocytes. Increased Ca<sup>2+</sup> levels stimulate reactive oxygen species and there is a bidirectional interaction between these parameters (2). It has been reported that trimetazidine shows cardioprotective effects by decreasing the intracellular calcium accumulation by controlling the membrane ion gradients (3). It has been shown that caspase 3 and caspase 9 activities play an important role in mitochondrial apoptotic pathways (4). Lui et al. (5) showed that trimetazidine pretreatment could attenuate myocardial apoptosis and improve cardiac function by decreasing apoptotic rate and the expression levels of cleaved caspase 3 and 9.

Therefore, we think that measuring the aforementioned parameters, such as intracellular calcium levels and caspase 3 and caspase 9 activity, could provide insights into the cardioprotective role of trimetazidine in chemotherapy-induced cardiotoxicity.

 Murathan Küçük,  Can Ramazan Öncel<sup>1</sup>

<sup>1</sup>Department of Cardiology, Faculty of Medicine, Akdeniz University; Antalya-Turkey

<sup>2</sup>Department of Cardiology, Faculty of Medicine, Alanya Aladdin Keykubat University; Antalya-Turkey

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**Address for Correspondence:** Dr. Can Ramazan Öncel, Alanya Aladdin Keykubat Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Antalya-Türkiye  
Phone: +90 506 371 51 99  
E-mail: r\_öncel@hotmail.com - can.öncel@alanya.edu.tr  
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## Author's Reply

To the Editor,

I appreciate his interest in my study (1). He has pointed out about the rationalization of the concentrations of trimetazidine (200 µM) and coenzyme Q10 (200 mg/L) used in the ventricular myocytes. I performed the preliminary experiments to analyze the responses of rat cardiomyocytes to serial doses of TMZ (12.5–200 µM) or CoQ10 (12.5–200 mg/L). TMZ or CoQ10 attenuated cisplatin-induced cell toxicity in a dose-dependent manner using a CCK8 assay. However, statistical significance was only observed at a concentration of 200 µM TMZ or 200 mg/L CoQ10. Therefore, I chose to use 200 µM TMZ and 200 mg/L CoQ10 for subsequent experiments.

He has recommended measuring parameters, such as intracellular calcium levels and caspase 3 and caspase 9 activities. These parameters could be useful to investigate the mechanisms of the cardioprotective role of trimetazidine in chemotherapy-induced cardiotoxicity; however, my study focused on the upstream of caspase activities as described in the paper's introduction. ROS-mitochondrial dysfunction-Nrf2/CytoC-apoptosis was the major framework of my study. On the other hand, caspase-dependent apoptosis has been briefly dealt with in the paper's introduction and discussion.

 Li Zhao

Department of Cardiology, Obstetrics and Gynecology Hospital of Fudan University; Shanghai-China

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**Address for Correspondence:** Li Zhao, MD, Department of Cardiology, Obstetrics and Gynecology Hospital of Fudan University; No. 419, Fangxie Road, Huangpu District Shanghai-China  
Phone: 86-21-33189900  
E-mail: zhaoli20181212@163.com  
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