

Angiogenin and osteopontin and coronary collateral circulation

To the Editor,

We read the publication on “The association between serum angiogenin (AGN) and osteopontin (OPN) levels and coronary collateral circulation in patients with chronic total occlusion” with a great interest. Gürses et al. (1) concluded that “AGN and OPN are associated with better developed coronary collateral circulation and may have therapeutic implications for the promotion of coronary collateral development” and also noted that “the underlying mechanisms remain largely unknown”. We would like to share our ideas on this report. First, the results in this study inconsistent with those reported previously, which demonstrated that AGN level was associated with complications of acute coronary syndrome and AGN was not a marker for revascularization or collateral circulation formation (2). The adjustment for the background of the patients in both the groups might help increasing the clarity of the findings. Certainly, many possible background conditions might affect the result of AGN investigation. For example, the underlying genetic hemoglobin disorders might result in a high AGN level regardless of the occurrence of the acute coronary syndrome or collateral circulation formation (3). In addition, the use of an ACE inhibitor, which is a common drug in the patient with cardiovascular disease, can also affect the level of OPN (4). We agree with the conclusion by Gürses et al. (1) that there might be an unknown mechanism linking AGN or OPN and collateral circulation formation, but there is a possibility that there might be interference or background factors that can alter the AGN or OPN level.

 Joob Beuy,  Viroj Wiwanitkit¹

Sanitation 1 Medical Academic Center; Bangkok-Thailand

¹Department of Community Medicine, Dr. DY Patil University; Pune-India

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Address for Correspondence: Joob Beuy, MD,

Sanitation 1 Medical Academic Center;

Bangkok-Thailand

Phone: 6624658292

E-mail: beuyjoob@hotmail.com

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Author's Reply

To the Editor,

We thank the authors for their interest and comments on our manuscript titled “The association between serum angiogenin (AGN) and osteopontin (OPN) levels and coronary collateral circulation in patients with chronic total occlusion” (1).

The authors have claimed that the results of our study were not compatible with the findings of a previous study. However, Tello-Montoliu et al. (2) primarily investigated the prognostic role of AGN in acute coronary syndrome (ACS) patients. They did not explore or comment on the relationship between AGN and coronary collateral circulation. In fact, Tello-Montoliu et al. (2) emphasized that AGN may have a role in the development of microvessels in the core of atherosclerotic plaques as “a potent angiogenic growth factor” and thereby affect the prognosis of ACS patients. In addition, there is strong evidence in the literature regarding the angiogenic potential of AGN, which further support our findings (3, 4).

The authors have also claimed that there may be some background conditions that might affect the result of AGN investigation, such as “genetic hemoglobin disorders” or “use of some drugs”. In the Methods section of our paper, we had already explained that we excluded patients with systemic diseases. In addition, when the prevalence of these genetic disorders is considered, it is unreasonable to assume that these can significantly affect the results of a study with 122 participants. We had also provided data for the medications of participants in Table 3, and there was no difference with respect to the use of renin-angiotensin system (RAS) blockers between poor and better developed collateral groups. Therefore, a confounding effect of RAS blockers does not exist in our study.

From our point of view, the authors' claims those attribute our findings to “interference or background factors” are speculative and do not have a firm basis.

 Kadri Murat Gürses,  Muhammed Ulvi Yalçın¹,

 Duygu Koçyiğit²

Department of Basic Medical Sciences, Faculty of Medicine, Adnan Menderes University; Aydın-Turkey

¹Department of Cardiology, Faculty of Medicine, Selçuk University; Konya-Turkey

²Cardiology Clinics, Afyonkarahisar Dinar State Hospital; Afyonkarahisar-Turkey

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Address for Correspondence: Dr. Muhammed Ulvi Yalçın, Selçuk Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Konya-Türkiye
Phone: +90 332 221 00 00
Fax: +90 332 323 67 23
E-mail: ulviyalcin@gmail.com
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Methodological problems in the measurement of interleukin-33 concentrations in patients with heart failure with a reduced ejection fraction

To the Editor,

We have read manuscript entitled "The concentration of interleukin-33 (IL-33) in heart failure with reduced ejection fraction. *Anatol J Cardiol* 2019; 21: 305-13" with great interest (1). The study included 155 patients with heart failure and 60 healthy individuals to compare IL-33 levels (1). The authors pointed out that blood samples collected from patients on admission were stored at -80 °C until further use; however, they did not mention about blood sample storage time comparison between the patient and the control group. Storage time for blood samples may affect IL-33 concentration measurement and change results; for example, variable cytokine concentration levels were seen with different blood storage durations in the previous study (2).

The authors used the legend max human IL-33 kit manufacturer system as seen in the standard range of 15.6–1000 pg/mL, and the limit of detection is 4.14 pg/mL; it is not clear how values below this level are measured (3). However, the authors measured a healthy human concentration of 16.91 (0–81) pg/mL in Figure 1a, which we consider as an important problem as to how the kit measured levels below the limit of detection. Values between the limit of quantification and the limit of detection should be given qualitatively and calculated separately. Furthermore, we think that statistical measurement and interpretations made without value and corrections may affect the results.

Figure 1b is given as an interquartile range in figure legends, but that is not found in the text or figure. No numerical value was given in the text or figure for Figure 1c. In addition, the median was given in Figure 1d, and it was observed that the median value was below the limit of quantification.

Therefore, we think that the interpretations made on IL-33 in Figure 1a–1d are insufficient due to the methodological approach, and that the statistical comments about the values will seriously reduce the reliability. Furthermore, how values <4.14 are measured raises considerable doubt as they are below the minimum measurable limit.

The aim of the present study was to investigate the effect of cytokine expression on the course of the disease in patients with heart failure. However, case-control studies do not provide information about the course of the disease. These studies can only comment on the instant situation. To do this, we think that evaluation with longitudinal cohort studies would be a more appropriate method.

 Berhan Keskin,  İsmail Balaban,  Seda Tanyeri,  Özgür Yaşar Akbal,  Ali Karagöz

Department of Cardiology, Koşuyolu Kartal Heart Training and Research Hospital; Istanbul-Turkey

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Address for Correspondence: Dr. Berhan Keskin, Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü, Denizer Cad. Cevizli Kavşağı No: 2, Kartal, İstanbul-Türkiye
Phone: +90 537 977 67 36
E-mail: bekeskin@ku.edu.tr

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