Samim Emet, Murat Köse*, Timur Selçuk Akpınar*, Esra Yıldız[1], Tufan Tükek*
Departments of Cardiology, *Internal Medicine, Faculty of Medicine, İstanbul University; İstanbul-*Turkey*
[1]Clinic of Internal Medicine, Okmeydanı Education and Research Hospital; İstanbul-*Turkey*

References

1. Yıldız E, Köse M, Yürüyen G, Akpınar TS, Emet S, Erdem E, et al. Relationship between brain natriuretic peptide, microalbuminuria, and contrast-induced nephropathy in patients with acute coronary syndrome. Anatolian J Cardiol 2014; 14: 505-10. **[CrossRef]**
2. Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents. N Engl J Med 1994; 331: 1449-50. **[CrossRef]**
3. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 1989; 320: 143-9. **[CrossRef]**
4. Schwab SJ, Hlatky MA, Pieper KS, Davidson CJ, Morris KG, Skelton TN, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. N Engl J Med 1989; 320: 149-53. **[CrossRef]**
5. Kolonko A, Kokot F, Wiecek A. Contrast-associated nephropathy-old clinical problem and new therapeutic perspectives. Nephrol Dial Transplant 1998; 13: 803-6. **[CrossRef]**

Address for Correspondence: Dr. Samim Emet,
İstanbul Üniversitesi İstanbul Tıp Fakültesi
Kardiyoloji Anabilim Dalı, İstanbul-*Türkiye*
Phone: +90 212 414 20 00
Fax: +90 212 531 38 79
E-mail: samim03@hotmail.com

Additional diagnostic parameter for coronary artery disease during exercise test: Heart rate recovery

To the Editor,

We read with great interest the manuscript written by Akyüz et al. (1), entitled "Heart rate recovery may predict the presence of coronary artery disease," in the June issue of Anatolian Journal of Cardiology 2014;14:351-6. In that study, they investigated whether post-exercise first-minute abnormal heart rate recovery (HRR1) helps to predict the presence and severity of coronary artery disease (CAD) (1). They found that abnormal HRR, which was defined as ≤21 beats in the sitting position during the first minute of the recovery period, had moderate sensitivity and low specificity for predicting the presence of CAD. However, abnormal HRR was not predictive of the severity of CAD.

HRR after graded exercise is one of the commonly used parameters to reflect autonomic activity. Abnormal HRR might be attributable to a defect in sympathetic withdrawal, parasympathetic reactivation, or both. Because these changes correlate with an increased risk of death, it has been hypothesized that an abnormal HRR would similarly predict increased mortality. Chaitman et al. (2) showed that the mechanism of increased mortality associated with abnormal HRR might be related more to autonomic dysfunction than to the presence or extent of CAD. On the other hand, Kizilbash et al. (3) suggested that blunted HRR was associated with several risk factors of CAD. In addition, Gera et al. (4) found that abnormal HRR was also associated with a high prevalence of CAD, left ventricular dysfunction, and composite high-risk myocardial perfusion imaging findings. In concordance with the basic findings of the study by Akyüz et al. (1), they also suggested that abnormal HRR alone, noted on stress testing, might warrant further evaluation for suspected CAD. When this relationship of abnormal HRR with CAD is taken in an opposite way, there are studies supporting this relationship. It has been shown that various programs that have been performed to control underlying CAD or rehabilitation of a CAD patient improve HRR. Tsai et al. (5) found that patients who were enrolled in a cardiac rehabilitation program after undergoing coronary artery bypass graft surgery had significantly higher HRR values compared to the control group.

In conclusion, although HRR and CAD prediction are and will further be a topic of hot debate, such an index, which can very easily be obtained during exercise stress test, can be used as a diagnostic parameter, in addition to the more commonly used parameters, including ST-segment depression, typical chest pain, or hypotensive response.

Uğur Nadir Karakulak, Naresh Maharjan[1], Engin Tutkun*, Ömer Hınç Yılmaz*
Departments of Cardiology and *Clinical Toxicology, Ankara Occupational Diseases Hospital; Ankara-*Turkey*
[1]Department of Cardiology, Faculty of Medicine, Hacettepe University; Ankara-*Turkey*

References

1. Akyüz A, Alpsoy S, Akkoyun DC, Değirmenci H, Güler N. Heart rate recovery may predict the presence of coronary artery disease. Anatolian J Cardiol 2014; 14: 351-6. **[CrossRef]**
2. Chaitman BR. Abnormal heart rate responses to exercise predict increased long-term mortality regardless of coronary disease extent: the question is why? J Am Coll Cardiol 2003; 42: 839-41. **[CrossRef]**
3. Kizilbash MA, Carnethon MR, Chan C, Jacobs DR, Sidney S, Liu K. The temporal relationship between heart rate recovery immediately after exercise and the metabolic syndrome: the CARDIA study. Euro Heart J 2006; 27: 1592-6. **[CrossRef]**
4. Gera N, Taillon LA, Ward RP. Usefulness of abnormal heart rate recovery on exercise stress testing to predict high-risk findings on single-photon emission computed tomography myocardial perfusion imaging in men. Am J Cardiol 2009; 103: 611-4. **[CrossRef]**
5. Tsai SW, Lin YW, Wu SK. The effect of cardiac rehabilitation on recovery of heart rate over one minute after exercise in patients with coronary artery bypass graft surgery. Clin Rehabil 2005; 19: 843-9. **[CrossRef]**

Address for Correspondence: Dr. Uğur Nadir Karakulak,
Ankara Meslek Hastalıkları Hastanesi, Kardiyoloji Bölümü
P.O: 06100 Sihhiye/Ankara-*Türkiye*
Phone: +90 312 580 83 95
Fax: +90 312 580 84 04
E-mail: ukarakulak@gmail.com

Author`s Reply

To the Editor,

We would like to thank the authors for their comments on our original investigation published in the Anatolian Journal of Cardiology 20142014;14:351-6. (1). We defined abnormal heart rate recovery (HRR)

as ≤21 beats during the first minute of recovery in a sitting position and found that abnormal HRR is sensitive with regard to the diagnosis of coronary artery disease (CAD) (76.1%) but does not exhibit good specificity (41.3%). We suggest that the presence of abnormal HRR (≤21 beats) in treadmill exercise testing should be considered an additional diagnostic criterion for the presence of CAD, and therefore, we agree that HRR should be incorporated into the interpretation of treadmill exercise testing (TET), in addition to other significant parameters, such as ST-segment depression, typical chest pain, or hypotensive response.

Normal parasympathetic reactivation is needed for the rapid decrease in heart rate following the cessation of exercise. Therefore, slow HRR after exercise has prognostic value for predicting cardiovascular mortality, regardless of the extent of coronary disease (2). However, several risk factors for atherosclerosis, especially metabolic syndrome components (3), advancing age (4), and chronic obstructive pulmonary disease (5), are important factors of decreased HRR. Because the risk factors mentioned above are also strongly associated with CAD, the calculation of HRR, as well as traditional markers of ischemic response during TET, could provide additional diagnostic information about the presence of CAD.

Aydın Akyüz
Department of Cardiology, Faculty of Medicine, Namık Kemal University; Tekirdağ-*Turkey*

References

1. Akyüz A, Alpsoy S, Akkoyun DC, Değirmenci H, Güler N. Heart rate recovery may predict the presence of coronary artery disease. Anatolian J Cardiol 2014; 14: 351-6. **[CrossRef]**
2. Chaitman BR. Abnormal heart rate responses to exercise predict increased long-term mortality regardless of coronary disease extent: the question is why? J Am Coll Cardiol 2003; 42: 839-41. **[CrossRef]**
3. Kizilbash MA, Carnethon MR, Chan C, Jacobs DR, Sidney S, Liu K. The temporal relationship between heart rate recovery immediately after exercise and the metabolic syndrome: the CARDIA study. Euro Heart J 2006; 27: 1592-6. **[CrossRef]**
4. Kligfield P, McCormick A, Chai A, Jacobson A, Feuerstadt P, Hao SC. Effect of age and gender on heart rate recovery after submaximal exercise during cardiac rehabilitation in patients with angina pectoris, recent acute myocardial infarction, or coronary bypass surgery. Am J Cardiol 2003; 92: 600-3. **[CrossRef]**
5. Inal Ince D, Savcı S, Arıkan H, Sağlam M, Boşnak Güçlü M, Tokgözoğlu L, et al. Cardiac autonomic responses to exercise testing in patients with chronic obstructive pulmonary disease. Anatolian J Cardiol 2010; 10: 104-10. **[CrossRef]**

Address for Correspondence: Dr. Aydın Akyüz,
Hürriyet Mah. Şehit Gökmen Yavuz Cad.
No=2/1, Tekirdağ-*Türkiye*
Phone: +90 282 261 10 58
E-mail: ayakyuzq5@gmail.com

Assessment of serum hepcidin levels in patients with non-ST elevation myocardial infarction

To the Editor,

We read the article, entitled "Assessment of serum hepcidin levels in patients with non-ST elevation myocardial infarction," by Altun et al. (1) published in Anatolian J Cardiol 2014; 14: 515-8. Serum hepcidin levels were comparable among NSTEMI patients and control subjects. Also, its concentration did not change 6 hours after admission. The authors concluded that hepcidin could not be used as a marker of myocardial necrosis in NSTEMI patients. We thank the authors for drawing attention to a very important and challenging field of cardiology: markers in acute coronary syndromes. However, in their study, we think that there are some important questions that need to be answered.

The peptide hormone hepcidin is the main conductor of systemic iron hemostasis (2). The expression of the hepcidin gene has been shown to be regulated by hypoxia and inflammation (3). According to this finding, Suzuki et al. (4) argued that the human heart might also react to ischemia, and they measured serum hepcidin levels in patients with acute myocardial infarction. They found an elevated serum hepcidin level within 4 hours after the heart attack and showed that hepcidin levels decreased to normal levels in 7 to 14 days. In the present study of Altun et al. (1) the time interval between the onset of the symptoms and blood sampling was not mentioned. Additionally, the authors retested serum samples of the NSTEMI patients only 6 hours later. However, hepcidin levels are detectable after several days following myocardial injury (4). The racial and genetic differences between the study population of Suzuki et al. (4) and Altun et al. (1) can explain the negative result of the latter study. The authors did not mention anything regarding coronary artery lesions of the study population; control subjects were aged between 50 and 70 years, and they can also have coronary atherosclerosis. Hence, it is an important limitation of this study if hepcidin might reflect destabilization of the coronary plaques, as expected from an inflammatory biomarker. The authors provided that CRP levels were increased in NSTEMI patients. In this point, performing a correlation analysis between CRP and hepcidin levels is very essential. In the case of showing this relationship, it could be argued that hepcidin might be a surrogate marker of inflammation, although plasma kinetics were not identified properly. Moreover, since this biopeptide is not a structural element of the myocardial cell like cardiac troponin I, it naturally might not be elevated at the same time. Finally, serum levels of hepcidin in patients and in control subjects were unevenly distributed: 24.55±32.13 and 23.67±33.62 ng/mL. It can be concluded that there are many extreme cases in the laboratory results, which can affect all analyses and interpretations in this small-sized study.

Therefore, we think that although the study conducted by Altun et al. (1) draws attention to a very important and interesting subject, there are several points in the study design and data evaluation that need to be discussed, and the study results should be interpreted with caution.

Kaan Okyay, Aylin Yıldırır
Department of Cardiology, Faculty of Medicine, Ankara Training and Research Hospital, Baskent University; Ankara-*Turkey*

References

1. Altun B, Altun M, Acar G, Kılınç M, Taşolar H, Küçük A, et al. Assessment of serum hepcidin levels in patients with non-ST elevation myocardial infarction. Anatolian J Cardiol 2014; 14: 515-8. **[CrossRef]**
2. Ruchala P, Nemeth E. The pathophysiology and pharmacology of hepcidin. Trends Pharmacol Sci 2014; 35: 155-61. **[CrossRef]**
3. Merle U, Fein E, Gehrke SG, Stremmel W, Kulaksız H. The iron regulatory peptide hepcidin is expressed in the heart and regulated by hypoxia and inflammation. Endocrinology 2007; 148: 2663-8. **[CrossRef]**
4. Suzuki H, Toba K, Kato K, Ozawa T, Tomosugi N, Higuchi M, et al. Serum hepcidin-20 is elevated during the acute phase of myocardial infarction. Tohoku J Exp Med 2009; 218: 93-8. **[CrossRef]**