Hemodialysis International 2011; **15**:581–582

Letters to the Editor

Ventricular arrhythmia: A new explanation for hemoglobin paradox in end-stage renal disease?

To the Editor:

I read with great interest the article describing the various risk factors of ventricular arrhythmia in hemodialysis patients by Saygi et al. in the April issue of *Hemodialysis International*.[1] By using a Holter monitor continuously for 48 hours and echocardiography, Saygi et al. have successfully illustrated that higher hemoglobin level is associated with higher frequency of ventricular premature complex (VPC). Their study is impressive despite the fact that no hard outcome was measured, and I would like to present another view of this article.

The fact that the normalization of hemoglobin level in patients with end-stage renal disease does not enable better survival is not new, but the mechanism had been ambiguous until Szczech et al., who attributed this risk of low hemoglobin levels to the administration of a high dose of erythropoietin.[2] Subsequent observational studies have largely supported this finding; Regidor et al. proposed a "reverse J-curve" to describe the hemoglobin–mortality curve.[3] Further, Solomon et al., in their recent Trial to Reduce Cardiovascular Events with Aranesp Therapy study, point out that patients with a lower hemoglobin response to darbepoietin alfa (Aranesp) therapy and receiving higher doses of darbepoietin alfa have higher mortality rates or cardiovascular events than patients that manifest a better hemoglobin response.[4] The estimated mortality hazard ratio is 1.23 per 1000 unit increase of erythropoietin dosage.[5] Overall, these studies signify the importance of erythropoietin dosage and underlying hemoglobin responsiveness, which may affect patient-level outcomes. The population characteristics in the study by Saygi et al. showed compatibility with the previously mentioned overall observation. Despite all these studies and observed facts, within this controversial hemoglobin paradox, we have only discovered the detrimental effects of a higher erythropoietin dose and lower hemoglobin responsiveness; however, the holy grail between dose and mortality has not been found yet. Because arrhythmia is a cause of cardiovascular disease and overall patient mortality, a higher rate of ventricular arrhythmia presenting as increased VPC frequency may be a reasonable connection between the proposed fact of higher dosage and higher mortality. Although the administration of erythropoietin has demonstrated a cardioprotective effect in animal models of acute myocardial infarction and reduced the frequency of ventricular arrythmia,[6] a completely different situation would be expected in dialysis patients, similar to the "paradox" mentioned previously. Further investigation is required to understand the exact mechanism; however, I believe that the study by Saygi et al. has already resolved part of the paradox.

For further refining their results, I believe that Saygi et al. should clarify the ultrafiltration rate and volume in the hemodialysis study population, because a higher rate of ultrafiltration will undoubtedly further increase the hemoglobin level of each individual after single dialytic session, notwithstanding the effect on patients with higher hemoglobin response. The rate of ultrafiltration may in fact play a significant role in this heightened risk in the higher hemoglobin responsive group, because patients of this group may have a certain degree of silent myocardial ischemia from the transient normalization of hemoglobin level near the end of dialytic session, presenting as ventricular instability. Considering the cardiovascular risk profile of the higher hemoglobin responsive group, this factor should be analyzed before considering arrhythmia

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DOI:10.1111/j.1542-4758.2011.00583.x

as the predominant cause of increasing mortality in these patients.

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Manuscript received May 2011; revised July 2011.

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