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### Whole Blood Viscosity and Cardiovascular Diseases: A Forgotten Old Player of the Game

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We read the recently published article by Ozcan Cetin et al. [1] entitled ‘The forgotten variable of shear stress in mitral annular calcification: whole blood viscosity’ with great interest. In their very well-designed and presented paper the authors tried to assess the relationship between mitral annular calcification (MAC) and estimated whole blood viscosity (eWBV). They demonstrated that eWBV values were significantly high in patients with MAC. Multivariate analysis showed that WBV of both shear rates was an independent predictor of MAC. Using the ROC curve, a cut-off value of 70.1 for WBV at a low shear rate had a sensitivity of 83.7% and a specificity of 73.7%, while at a cut-off value of 17.5 at a high shear rate had a sensitivity of 79.6% and a specificity of 74.4%.

Although MAC is believed to be a mostly benign process, recent evidence obtained from clinical studies suggests that it is independently associated with cardiovascular disease (CVD) events, heart failure and cardiovascular mortality. Although the pathogenesis of MAC has not yet been precisely elucidated, abnormalities of calcium and phosphate homeostasis, such as in chronic kidney disease (CKD) and end-stage renal disease, may contribute to its pathogenesis [2].

CKD is a major risk factor for the development of CVD, and the CVD mortality rate worldwide is much higher amongst CKD patients than in the general population. CKD is also associated with a higher rate of cardiovascular events (CVE) [3]. Endothelial dysfunction is the initial pathophysiological step in the progression of atherosclerosis that precedes and leads to clinically manifest CVD [3]. The pathophysiology of atherosclerosis is a complex multifactorial process, of which blood flow-induced shear stress may cause the endothelial dysfunction. Thus, shear stress, especially when blood flow is disturbed and/or is nonlaminar, plays a major role in the pathogenesis of the atherosclerotic plaque.

WBV is positively correlated with shear stress. It is a useful and practical method in clinical practice. Recent studies have shown that eWBV levels play a critical role in atherosclerosis [4]. WBV is associated with carotid thickening, suggesting that rheologic factors are involved in the subclinical phase of atherosclerosis. On the

other hand, there is increasing evidence that eWBV levels may be predictors of the risk of future CVD.

In our recently published clinical study we tried to investigate the relation between plasma eWBV levels and cardiovascular outcomes in patients with CKD [5]. We undertook a cross-sectional study with prospective follow-up including consecutive patients with CKD. Plasma eWBV levels were measured in 417 patients with newly diagnosed CKD. The study patients were divided into two groups consisting of those with and those without CVE. We also measured the estimated glomerular filtration rate (eGFR), markers of inflammation, pentraxin 3, high-sensitivity C-reactive protein and vascular abnormalities, including flow-mediated dilatation (FMD). All-cause mortality and CVE were also analyzed with respect to plasma eWBV. The eWBV levels were higher in the patients with CVE compared to those without CVE. Additionally, markers of inflammation were higher and FMD and eGFR were lower in the CVE group compared to those without CVE. WBV, plasma asymmetric dimethylarginine levels, FMD, high-sensitivity C-reactive protein, eGFR, systolic blood pressure, calcium and history of diabetes are all significant independent predictors of cardiovascular outcomes in patients with CKD. Kaplan-Meier survival curves were generated to establish the impact of WBV on the cumulative survival of the cohort. Patients with WBV values higher than 5.2 cP had lower survival rates compared to patients with WBV values lower than 5.2 cP (log-rank = 4.49, d.f. = 1, p = 0.034).

In conclusion, WBV is part of Virchow’s triad, including stasis, endothelial dysfunction and atherothrombosis, leading to cardiovascular complications. Indeed, WBV is an important index for stasis. When considering a high MAC prevalence in patients with CKD, we strongly believe that the current study reaffirmed the essential role of WBV in the pathophysiology of CVD.

#### References

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## Reply

### Disadvantages of Extrapolated Whole Blood Viscosity Formula among Patients with Chronic Kidney Disease

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We would like to thank Celik et al. for their considered comments about our recent paper [1]. As outlined in their letter, the prevalence of cardiovascular diseases is significantly higher in patients with chronic kidney disease compared to the general population [2]. There are several pathophysiological mechanisms which predispose these patients with CKD atherogenesis, including stasis, endothelial dysfunction and increased thrombogenicity. As we mentioned in our previous studies [1, 3], whole blood viscosity (WBV) can be simply extrapolated with a confirmed formula using hematocrit (HCT) and total protein levels. Because we know that patients with CKD might present with concomitant proteinuria according to the etiology of the disease, patients with CKD and renal failure were excluded [1, 3]. Another important point is the issue of increased viscosity after renal replacement therapy in stage 5 CKD due to increased HCT levels. The volume status of patients with CKD is another problem to be considered, which has an impact on both HCT and total protein levels and can lead to a misinterpretation of the WBV calculation. Therefore, care should be taken when interpreting extrapolated WBV levels in patients with CKD. Besides its advan-

tages, including its simple calculation, researchers should also comment on the technical disadvantages of extrapolated WBV in patients with CKD.

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