VIEWPOINT

Commentaries on Viewpoint: Anemia contributes to cardiovascular disease through reductions in nitric oxide

COMMENTARY ON VIEWPOINT: ANEMIA CONTRIBUTES TO CARDIOVASCULAR DISEASE THROUGH REDUCTIONS IN NITRIC OXIDE

TO THE EDITOR: More than five decades ago, it was demonstrated that local vascular resistance falls as \( P_{\text{O}_2} \) is decreased (2). Later, it was shown that NO dissociates faster from hemoglobin in the T-state than from the R-state (3), and this was done even before NO was appreciated as a biomolecule. These seemingly disparate observations only crystallized into a cogent mechanism when the SNO-hemoglobin paradigm was first introduced (4) and later confirmed (5). Now, Andreotti et al. (1) propose to build on this edifice to explain the increased mortality seen when cardiovascular disease (CVD) and anemia co-occur. They state: “... it is our viewpoint that a plausible interpretation of the data is that anemia contributes to CVD through reduced NO as well as reduced oxygen bioavailability.” This is an important conjecture, which if proven correct, could open promising new therapeutic pathways. However, it would be no simple matter to convert plausibility into fact that could be applied to human disease. The complex pathophysiology of CVD complicated by anemia would demand careful experimental measurements, initially in animal models, that only a few laboratories have, up to now, been able to make reproducibly. In addition, once the pathological processes are sufficiently elucidated, pharmacological strategies would need to be devised to replenish the missing NO bioactivity and deliver it in the right amounts, in the right places, and at the right times, all in the face of insufficient amounts of S-nitrosylated hemoglobin. Perhaps this Viewpoint will stimulate the research needed to make all this happen.

REFERENCES


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CAN EXERCISE IN HYPOXIA ALLEVIATE NO-DEPENDENT DETRIMENTAL EFFECTS OF ANEMIA?

TO THE EDITOR: The Viewpoint (1) clearly illustrates that low hemoglobin-related reductions in nitric oxide (NO) and \( O_2 \) avail-

ability, observed in anemic individuals, importantly contribute to cardiovascular disease. Indeed, reduced NO bioavailability leads to blunted vasodilation and can thus significantly limit local and systemic perfusion and \( O_2 \) delivery. Although authors (1) examine the influence of hypoxia on NO-related systemic vasodilation, little attention is given to potential effect of exercise. In particular, it is well established that exercise augments systemic NO bioavailability and thereby modulates vasodilation, mostly by repeated shear stress of the vasculature and upregulation of eNOS protein expression (5). Interestingly, the exercise-induced increase in NO bioavailability is most prominent in individuals with preexisting endothelial dysfunction, often associated with cardiovascular disease (5). Performing exercise in hypoxia further augments flow-mediated vasodilation via increased NO activity to compensate for the decreased \( O_2 \) availability and match \( O_2 \) supply to demand (2). Although hypoxia per se elicits oxidative stress (potentially leading to reduced NO bioavailability), we recently showed that 2 h of moderate daily exercise can offset hypoxia-induced oxidative stress (3). Taken together, these data suggest that combining exercise and hypoxia/altitude exposure might be a viable strategy to counteract anemia-provoked reductions in NO availability and consequently reduce anemia-related cardiovascular risk. However, given that differential effects of hypobaric and normobaric hypoxia on NO modulation have previously been identified (4), further clinical investigations are warranted to elucidate optimal combination of exercise and hypoxia (dose/type) for alleviating NO-dependent detrimental effects of anemia and other chronic ailments.

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TO THE EDITOR: Andreotti et al. (1) build their hypothesis that anemia is related to cardiovascular morbidity through limited NO availability partly on our study on flow-mediated vasodilation (FMD) (2). In normal subjects, FMD was inversely related to artery diameter and the Hgb concentration, but we specifically tested if the Hgb concentration and the basal artery diameter were correlated: They were not, and hence we could not see evidence suggesting that the basal rate of NO was related to the Hgb concentration. What we demonstrated was a more pronounced radial artery FMD with Hgb concentration <14 g/dl, and although our study was cross-sectional in nature, and hence could not prove it, we in fact actively considered the opposite hypothesis of Andreotti's, i.e., little absorbance by Hgb = more freely available NO = more pronounced FMD (2). In vitro, Hgb absorbs NO, and in earlier years NO-mediated vasodilation was considered an “on-off” response, but early an injected bolus of NO could be detected far from its injection site (and hence absorbance by Hgb could not be as quick/complete as initially suggested), and the Stamler hypothesis (3) does indeed suggest that NO can be “ferried,” but perhaps absorbance by Hgb (also within the normal range) is simply “graded.” So-called type II acute myocardial infarctions, contributing to the added cardiovascular disease burden of anemia, are often seen, but hardly ever in young patients, far more often in elderly atheromatotic patients, and hence most often probably related to already maximal vasodilation in stenosed coronary arteries.

REFERENCES

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