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Anemia and Acute Coronary Syndrome: Time for Intervention Studies

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Originally characterized as "globules of his blood" in 1675 by the Dutch microscopist van Leeuwenhoek, the crucial role of erythrocytes, or red blood cells, in regulating normal human physiology was not appreciated until centuries later.[1] In contemporary medical taxonomy, the construct of anemia equates to a reduction in red blood cell mass and the diagnosis is established using convenient sex-specific thresholds set forth by the World Health Organization: hemoglobin level <13 g/dL for men and <12 g/dL for women.[2] Such a standardized schema facilitates not only clinical investigation surrounding the determinants and impact of anemia but also enables the development of therapeutic strategies to treat such patients. It is within this context that Mamas et al have examined the prevalence, correlates, and associations between anemia and subsequent cardiovascular risk in a large retrospective cohort of patients presenting with acute coronary syndromes (ACS).

The authors queried a large database of over 40 000 ACS patients admitted to hospitals in England and Wales between 2006 and 2010 with follow-up to 2011.[3] Salient findings from this investigation include an overall prevalence of anemia approximating 28% and substantial differences in both the profile and management of patients with versus without anemia. For example, patients with anemia had more comorbidities, were less likely to receive coronary angiography, and to receive dual antiplatelet as well as secondary prevention therapy on discharge compared with their counterparts showing normal hemoglobin levels. Several factors were independently associated with anemia (eg, age, sex, smoking, hyperlipidemia, angina, previous myocardial infarction, previous heart failure, previous stroke, peripheral vascular disease, diabetes mellitus, chronic obstructive pulmonary disease, renal disease, previous coronary intervention, admission on clopidogrel, and aspirin). With respect to short-term and longitudinal outcomes, the authors demonstrate an independent association between the presence of anemia and both 30-day and 1-year mortality. Findings were consistent irrespective of ACS type, sex, and in patients with and without bleeding complications during the index hospitalization. Their results were robust due to a variety of statistical approaches to account for the marked differences in patient profiles with versus without anemia.

While any observational study is inherently limited by selection bias and the potential for both residual and unmeasured confounding, the analysis by Mamas et al is strengthened by its large, representative sample, consistent results across different subgroups and analytic approaches, and inclusion of a contemporary cohort, thereby enhancing generalizability to current practice. These results extend and are largely consistent with earlier observations documenting a high prevalence of anemia in both heart failure and ACS.[4] Others have also shown excess risk associated with anemia in the setting of ACS.[5–7] These findings, in concert with earlier studies, lead to several natural questions with important clinical impact. First, how does anemia influence cardiovascular risk and secondly, how can such risk be mitigated?

With respect to the former, several hypotheses may account for a direct and causal effect between anemia and mortality. First, the sine qua non of ACS is an imbalance between myocardial oxygen supply and demand, and the presence of anemia further potentiates this imbalance both by reducing oxygen-carrying capacity and simultaneously increasing myocardial oxygen consumption via increased cardiac output (Figure). Secondly, experimental data suggest an impaired capacity for vascular healing among ACS patients with anemia.[8] Third, inflammatory flux is inversely related to hemoglobin levels in ACS patients, which may further confer increased risk.[9] While such mechanisms may account for short-term hazards, the findings by Mamas et al and others

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highlight much more durable and long-term links between anemia and adverse cardiovascular events. In part, long-term risks may be mediated by pathologic changes in inflammatory, thrombotic, or other pathways that influence atherothrombosis. The provision of fewer and less intense medications, or confounding by indication, may also result in greater cardiac risk among patients with anemia. Finally, anemia may serve as an efficient biomarker of long-term risk in the absence of any direct mediating effects.

Notwithstanding the importance of pathologic mechanisms, equally if not more important are treatments to improve the outcomes of patients with anemia. In this regard, the results of formal experimental and observational studies to date have been sobering. Blood transfusions have well-documented side effects including transfusion reaction, increased systemic inflammation, and erythrocyte slugging in capillary vessels.[10,11] Randomized studies comparing different transfusion thresholds failed to show any advantage with a more liberal cut-off of 9 to 10 g/dL, substantiating current recommendations to transfuse at more restrictive levels of 7 to 8 g/dL.[12–15] Another strategy involves the administration of erythropoietin, a hematopoietic hormone produced by the kidneys in response to hypoxia,[16] which was hypothesized to improve outcomes in patients with ACS. However, studies investigating the injection of erythropoiesis-stimulating agent (eg, erythropoietin) in ST-segment elevation myocardial infarction patients failed to show a benefit, with at least 1 study demonstrating an increased risk of death, myocardial infarction, and stroke associated with such therapy.[16,17] In contrast, intravenous iron substitution did improve functional capacity and quality of life in anemic patients with heart failure.[18] However, no data are available to provide a recommendation for treatment of iron deficiency in the setting of ACS.

How then should a clinician approach an ACS patient with concomitant anemia? As recommended by current American College of Cardiology/American Heart Association guidelines, measures should be taken to minimize risks for bleeding. This may be accomplished by integrating formal bleeding risk algorithms within usual care pathways to identify patients who will derive the greatest benefit from bleeding avoidance strategies, such as transradial access and use of vascular closure devices. Dosing of antithrombotic therapy by weight and renal function should be emphasized to further minimize bleeding risks. With respect to treatment, a restrictive transfusion threshold of 8 g/dL appears reasonable given the potential for harm with administration of blood products coupled with the lack of any clear benefit in randomized studies using a more liberal threshold.

Our understanding of red blood cells, both in normal human physiology and in disease states, has advanced substantially since the seminal observations of van Leeuwenhoek. While we currently appreciate the prognostic

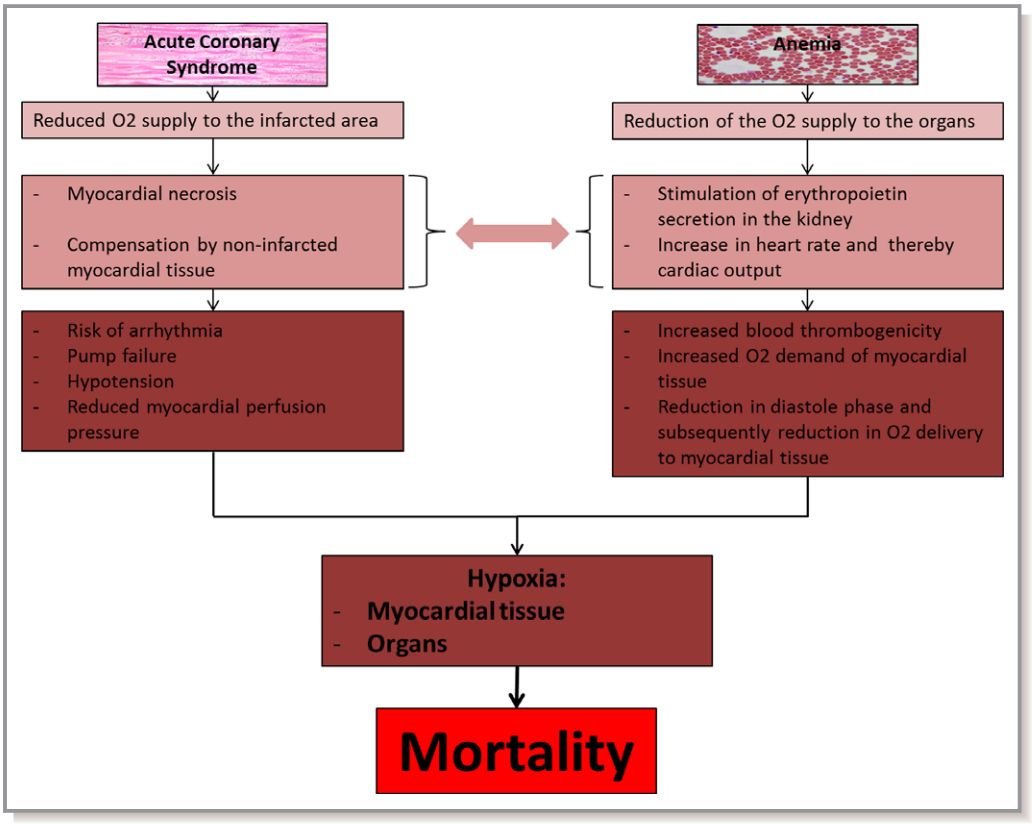

Figure. Pathophysiological mechanisms in acute coronary syndrome and anemia.

importance of anemia on both short- and long-term outcomes following ACS, clear mechanistic insights and therapeutic interventions to guide and mitigate such risk remain lacking. The need for studies to inform clinical decisions within this space is highlighted by studies such as the one by Mamas et al, reinforcing the high prevalence of and substantial risk associated with anemia in the setting of ACS.

Disclosures

None.

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