Arterial Homeostasis, Inflammation, and Erythropoietic Growth Factors

Pascal J. Goldschmidt-Clermont, MD,* Anna Mae Diehl, MD†

Divisions of Cardiology* and Gastroenterology†, Department of Medicine, Duke University Medical Center, Durham, NC

A neurohumoral link between kidneys and the heart has been established, particularly in the context of hypertension and cardiomyopathy. Beyond this neuro-endocrine pathway, another connecting system theoretically recruits growth factors that are selectively produced by the kidneys and have the ability to promote a distant reaction at the level of bone marrow. This reaction differentiates and circulates vascular progenitor cells capable of repairing the injured cardiovascular system. Reducing injuries (prevention) stabilizes disease processes by reducing tissue damage and destruction but the gradual degradation of the body's natural repair mechanisms eventually allows progressive reactivation of disease processes. In this light, a focus on tissue repair rather than injury prevention may hold the key to controlling chronic heart diseases. This article examines the medical therapies, including recombinant human erythropoietin, that have been shown to improve the function and survival of endothelial progenitor cells and promote the healing of damaged tissue.

[Rev Cardiovasc Med. *2005;6(suppl. 3):S22-S26*]

Key words: Erythropoietin • Endothelial progenitor cells • Vascular endothelial growth factor

It is well recognized that maintenance of kidney function is relevant to cardiovascular health. Correspondingly, for patients with cardiovascular disorders, deterioration of kidney function is a strong, perhaps the strongest, marker of poor prognosis (Figure 1).[1] A neurohumoral link between kidneys and the heart has been established, particularly in the context of hypertension and cardiomyopathy. The renin-angiotensin-aldosterone system (RAAS) has long been associated with hemodynamic regulation and alteration of the

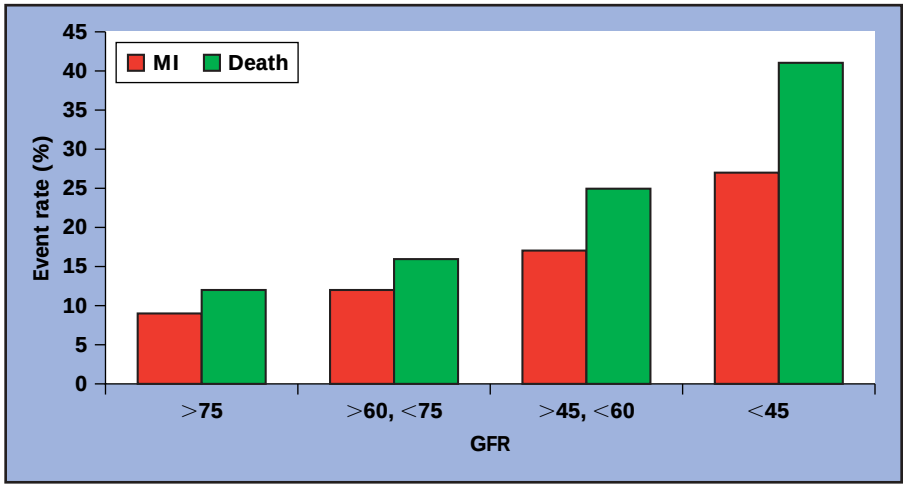


Figure 1. *Kaplan–Meier calculation of the rates of death from cardiovascular causes or reinfarction at 3 years in the Valsartan in Acute Myocardial Infarction Trial (VALIANT), according to estimated glomerular filtration rate (GFR, mL/min/1.73 m^2) at baseline. P (< .001) is derived from the Cox model used in this study. Patients (N = 14,527) had acute myocardial infarction (MI) complicated by clinical or radiologic signs of heart failure, left ventricular dysfunction, or both, and a documented serum creatinine measurement. Adapted from Anavekar et al.*[1]

cardiovascular system by remodelling. Antagonists of the RAAS, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), as well as aldosterone inhibitors, have proven beneficial for patients with hypertension and cardiomyopathies.[2] Hence, factors that provide acute lifesaving hemodynamic stabilization for individuals experiencing a hemorrhagic shock, may, when experienced chronically, have a deleterious impact on cardiovascular homeostasis in heart failure patients.

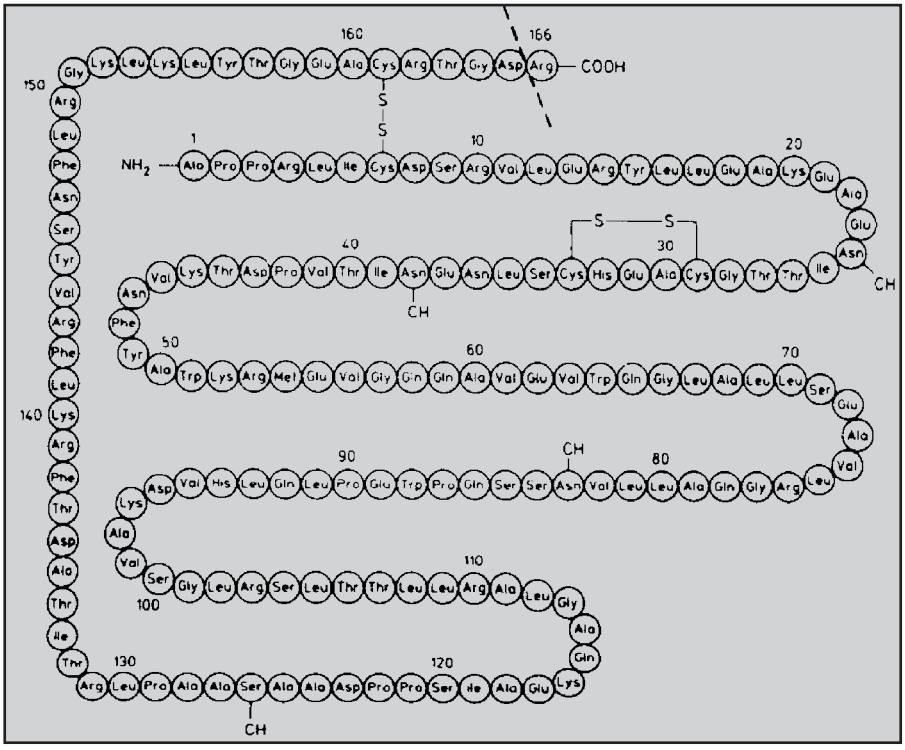
Cardiorenal Growth Factors

There appears to be another peripheral link between the kidneys and cardiovascular organs. Beyond the neuro-endocrine pathway, this connecting system theoretically recruits growth factors that are selectively produced by the kidneys and have the ability to promote a distant reaction at the level of bone marrow. This reaction differentiates and circulates vascular progenitor cells capable of repairing the injured cardiovascular system. Erythropoietin (EPO, Figure 2) is one of the growth factors produced primarily by the kidneys that can trigger a cellular progenitor response at the level of bone marrow.[3] Renal production of growth factors like EPO is critical to the ability of the cardiovascular system to maintain homeostasis (Figure 3). In order to understand this important link between kidney and cardiovascular structures, it is necessary to review recent findings in the field of vascular progenitor cells and their biology.

Injury Versus Repair in Tissue Damage

For years, the occurrence of common chronic diseases, such as coronary artery disease (CAD) or ischemic cardiomyopathy, was believed to result simply from the sustained impact of injurious factors (eg, smoking, abnormal circulating lipids) on arteries and other tissues.[4] The tissue response to such insults is generally well understood, with initial inflammation and cellular dysfunction

Figure 2. *Schematic presentation of the primary structure of human erythropoietin. Mature horm1 is composed of 165 amino acids, having lost carboxyterminal anginyl residue by posttranslational modification. There are 3 N-linked glycosylation sites (CH) at aspartyl residues 24, 38 and 83, and a U-linked glycosylation site (CH) at seryl residue 126. Reproduced, with permission, from Jelkmann.*[3]



followed by tissue remodeling. However, net end-organ damage is highly variable, both among individuals and within a given individual over the course of time. Thus, it remains difficult to predict disease prognosis and recommend appropriate treatment strategies.

The effect of aging on the outcomes of chronic diseases exemplifies the "disconnect" between injury and organ damage by showing that different degrees of tissue damage may result from similar levels of noxious exposures, even in a single individual.

The effect of aging on the outcomes of chronic diseases exemplifies the "disconnect" between injury and organ damage by showing that different degrees of tissue damage may result from similar levels of noxious exposures, even in a single individual. In youth, recurrent mild injuries seldom cause appreciable organ dysfunction.[5] With advancing age, however, disease typically becomes manifest, causing a state of generalized frailty, which is characterized by chronic inflammation, progressive inability to recover from minor injuries, and, eventually, multi-organ failure. Chronic inflammation by itself could impair the ability of bone marrow to mount an efficient repair response to arterial injury.[5,6] This age-related failure to cope with injuries is not generally due to progressive intensification of the noxious exposures themselves. Damage-provoking insults can be less intense over time, whereas disease propensity uniformly worsens with aging. The explanation for this paradox has only recently become apparent and it signals exciting new diagnostic and therapeutic opportunities.[5]

Scientists across multiple medical disciplines have demonstrated the fundamental importance of intrinsic repair processes, which constitutively erase all trace of injuries to organs during a lifetime.[5,7] Whereas the tissue in many adult organs (such as myocardium) was long thought to be fixed at birth, thereby precluding subsequent regeneration, new studies are demonstrating the remarkable ability of humans to repair and replace damaged cells throughout life. Cells responsible for this repair do not only originate from within damaged tissues. They are also recruited from more distant reservoirs of multipotent progenitors (such as bone marrow) by inflammation messengers and growth factors, including EPO and vascular endothelial growth factor (VEGF).[5,7-12] VEGF is a secreted protein with heparin-binding characteristics specific for vascular endothelial cells. It has been shown to induce angiogenesis in vivo.

Unfortunately, as we age, intrinsic obsolescence of such repair processes and dwindling repair capacity greatly impact the ultimate outcomes of chronic disorders.[5,7] When repair mechanisms are exhausted, recurrent injuries accelerate the natural senescence of tissues and the cells that compose them. In other words, tissue senescence leads to organ dysfunction unless counterbalanced by active repair and renewal of senescent cells. Innate or acquired obsolescence of the repair activities is sufficient to cause progressive, age-related deterioration of tissue integrity and function. Moreover, recurrent injuries that increase the burden of senescent cells tax repair mechanisms, thereby accelerating the natural evolution of organ damage and dysfunction. As it relates to the arterial tree, aging has been linked, particularly in the presence of risk factors, to established senescence and dysfunction of tissues and circulating endothelial progenitor cells (EPCs).[13,14]

This concept suggests that successful efforts to minimize damage in chronically injured tissues must incorporate strategies to improve repair. Reducing injuries (prevention) stabilizes disease processes by reducing tissue damage and destruction. However, gradual obsolescence of the repair mechanism typically progresses in such situations (perhaps due to repair-related consumption of progenitor cells), eventually permitting progressive reactivation of the disease process.[5,14]

The premise that the success of repair (rather than the severity of injury) dictates the ultimate degree of organ damage has broad implications. For example, certain ailments, such as autoimmune disorders, might target components of the repair process directly, thereby conferring susceptibility to a host of diseases at a relatively young age.[15] Alternatively, other inherited conditions might cause the degree of injury in cardiovascular tissues to be so substantial that repair mechanisms are overwhelmed early in life, promoting premature damage of other organs over time. Finally, it is conceivable that many successful therapeutic strategies for cardiovascular

Scientists across multiple medical disciplines have demonstrated the fundamental importance of intrinsic repair processes, which constitutively erase all trace of injuries to organs during a lifetime.

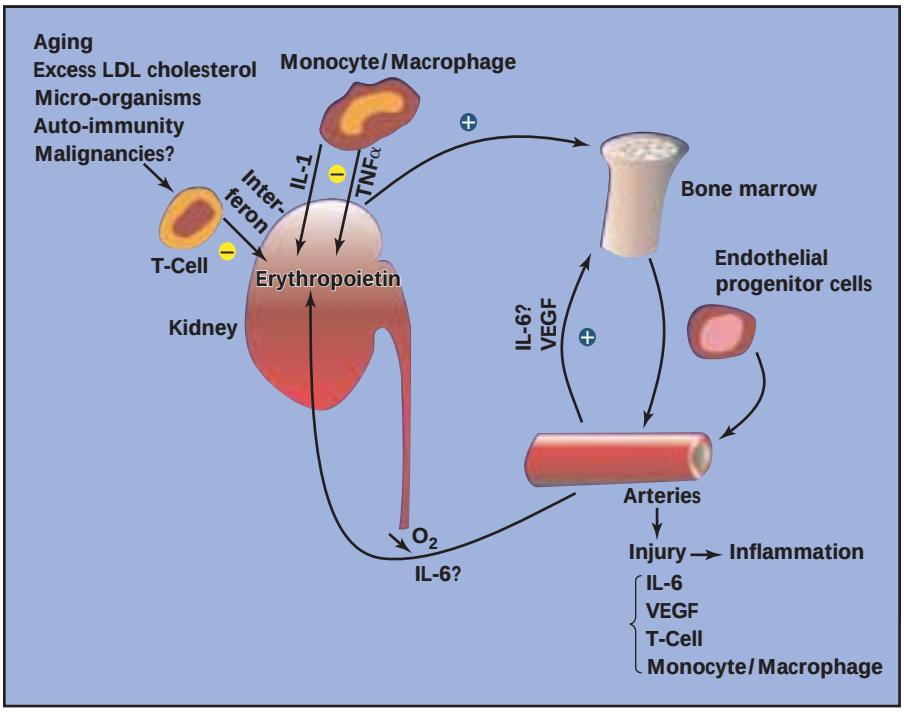


Figure 3. *Regulation of erythropoietin (EPO) production. Decreased PO_2 stimulates the production of EPO by the kidney. Some inflammatory cytokines can compromise such production (interferon$_8$, interleukin$_1$, tumor necrosis factor-α [TNFα]), whereas other cytokines may help increase production (interleukin6 [IL-6]). EPO stimulates the production of endothelial progenitor cells (EPC) via bone marrow, which in turn contributes to the repair of arteries.[16] Lack of EPC response may further aggravate the inflammatory milieu, which has a negative impact on EPO production. LDL, low-density lipoprotein.*

disease (eg, β-blockers, statins, aspirin) produce benefits that might be related to their impact on repair processes, including recruitment and/or differentiation of progenitor cells.

Improving Endothelial Progenitor Cell Function

Endothelial cells, which comprise the endothelium, or innermost layer of cells in blood vessels, are key to tissue repair in cardiovascular disease, as injury to endothelial cells stimulates the development of atherosclerotic plaques. These cells are generated from less developed predecessor cells, or endothelial progenitor cells (EPCs) that travel through blood vessels and replace lost or damaged endothelial cells, thus delaying atherosclerotic disease as well as promoting neovascularization of tissue post-ischemia.

Statins have been shown to have a positive impact on EPC function and survival. Statins have the ability to improve the life span and robustness of EPCs, apparently through activation of the AKT protein kinase pathway. In several models where the activity of EPCs could be tested in terms of capacity for arterial repair and angiogenesis, treatment of the model with statins led to improved function of EPCs.

Recombinant erythropoietins (epoetins) constitute a group of agents that can also improve the production of EPCs. These recombinant compounds lack carbohydrate moieties that are normally present in the native human hormone (Figure 2). In patients with chronic renal failure, epoetin has been shown to markedly enhance EPC proliferation and differentiation.[10-12] Epoetin appears to physiologically regulate EPC mobilization in patients with ischemic heart disease. In these patients, epoetin serum levels significantly correlate with the number of circulating EPCs. Furthermore, the administration of epoetin increases the number of functionally active EPCs by differentiation in vitro, in a dose-dependent manner, as assessed in cell culture and by tube formation assay. Like the statins, epoetin activates the AKT protein kinase pathway in EPCs.

The angiogenic potential of epoetin and VEGF were compared in an in vitro assay.[9] Both growth factors showed equal pro-angiogenic capacity when measured in vitro. Thus, in patients with reduced circulating EPCs and CAD, the administration of epoetin could potentially prove therapeutic, particularly where the availability of EPO could be limited, as in patients with pre-dialysis chronic kidney disease. The intriguing role of EPO in enhancing arterial repair of myocardial angiogenesis is currently being tested in clinical trials.

In patients with chronic renal failure, epoetin has been shown to markedly enhance EPC proliferation and differentiation.

Conclusion

A deeper understanding of repair processes and their role in the maintenance of vascular homeostasis will open new avenues for discovery in biomedical research. These discoveries will undoubtedly lead to the

development of therapeutic strategies impacting, with great efficacy, human welfare. ■

References

1. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;350:1285-1295.
2. McMurray JJV, Pfeffer MA. The year in heart failure. *J Am Coll Cardiol*. 2004;44:2398-2405.
3. Jelkmann W. Erythropoietin: Structure, control of production, and function. *Physiological Reviews*. 1992;72:449-489.
4. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115-126.
5. Goldschmidt-Clermont PJ, Peterson ED. On the memory of a chronic illness. *Sci Aging Knowledge Environ (SAGE KE)*. 2003;45:re8.
6. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005; 352:1011-1023.
7. Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, et al. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation*. 2003;108:457-463.
8. Van der Meer P, Voors AA, Lipsic E, et al. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. *J Am Coll Cardiol*. 2004; 44:63-67.
9. Jaquet K, Krause K, Tawakol-Khodai, et al. Erythropoietin and VEGF exhibit equal angiogenic potential. *Microvascular Research*. 2002;64:326-333.
10. Heeschen C, Aicher A, Lehmann R, et al. Erythropoietin is a potent physiologic stimulus for endothelial progenitor cell mobilization. *Blood*. 2003;102:1340-1346.
11. Bahlmann FH, de Groot K, Duckert T, et al. Endothelial progenitor cell proliferation and differentiation is regulated by erythropoietin. *Kidney Int*. 2003;64:1648-1652.
12. Bahlmann FH, de Groot K, Spandau J-M, et al. Erythropoietin regulates endothelial progenitor cells. *Blood*. 2004;103:921-926.
13. Chang E, Harley CB. Telomere length and replicative aging in human vascular tissues. *Proc Natl Acad Sci*. 1995;92:11190-11194.
14. Hill JM, Zalos G, Halcox JPJ, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*. 2003; 348:593-600.
15. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Experimental Med*. 2005;201:591-601.
16. Means RT, Krantz SB. Inhibition of human erythroid colony-forming units by γ interferon can be corrected by recombinant human erythropoietin. *Blood*. 1991;78:2564-2567.

Main Points

- For patients with cardiovascular disorders, deterioration of kidney function is a strong, perhaps the strongest, marker of poor prognosis.
- Beyond the neuro-endocrine pathway, another connecting system theoretically recruits growth factors that are selectively produced by the kidneys and have the ability to promote a distant reaction at the level of bone marrow.
- Erythropoietin (EPO) is one of the growth factors produced primarily by the kidneys that can trigger a cellular progenitor response at the level of bone marrow and renal production of growth factors like EPO is critical to the ability of the cardiovascular system to maintain homeostasis.
- With advancing age, disease typically becomes manifest, causing a state of generalized frailty, which is characterized by chronic inflammation, progressive inability to recover from minor injuries, and, eventually, multi-organ failure; this concept suggests that successful efforts to minimize damage in chronically injured tissues must incorporate strategies to improve repair.
- Recombinant erythropoietins (epoetins) constitute a group of agents that have been shown to improve the production of endothelial progenitor cells, thus promoting tissue repair in chronic heart disease.
- In an in vitro assay, the angiogenic potential of epoetin and vascular endothelial growth factor were compared and demonstrated equal pro-angiogenic capacity.