Two Sides of the One Coin—the Cardiac and Vascular System

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To the Editor: Erythropoietin, although cardiocytoprotective to redox challenge [1], demonstrates vascular dysfunction [2,3]. HIFalpha is also a key cardiocytoprotective hypoxic response factor [4] yet relates to vascular dysfunction [5]. These represent differential effects on the heart *versus* vascular system, including coronary vasculature (CAD) – same factor, two substrates. The obvious example derives from the renin-angiotensin system. Angiotensin II is cardiocytoprotective [4] yet is a target for hypertension and is atherogenic [6].

Proinflammatory cytokines neatly exemplify this functional substrate *partitioning*. Interleukin-6 [7], TNF [8], cardiotrophin-1 [9] are cardiocytoprotective. Conversely, interleukin-6 and TNFalpha accelerate atherosclerosis *via* inflammation [10]. Cardiotrophin-1 is also proatherogenic [11]. Interleukin-6 is hypertensive *via* an inflammatory mechanism [12]. CRP, a key factor mirroring inflammation, induces vascular dysfunction including coronary artery vasospasm [13] and hypertension [14] *via* interleukin-6. Under normoxia CRP does not adversely affect cardiomyocytes [15] though hypoxia may lead to induction of apoptosis.

Previous examples yield support for partitioning heart *versus* vasculature [16]. Sphingosine-1-phosphate is cardiocytoprotective [17] yet aids vascular dysfunction in hypertension [18]. Endothelin produces vascular dysfunction [19]. Statins act in part to moderate atherogenesis by endothelin reduction and improve endothelial physiology [20]. Conversely, endothelin is cardiocytoprotective [21]. Enolase is also cardiocytoprotective [22] yet associates with endothelial/vascular pathology [23]. Chromogranin is cardiocytoprotective [16] yet is overexpressed in hypertension [24] and associates with acute coronary syndromes [25]. MicroRNA21 is cardiocytoprotective [4,16]

yet relates to hypertension [26]. Tissue kallikrein, of which PSA is a family member, [16] is cardioprotective [27]. Notably, PSA has a role in preeclampsia [28] and relates to coronary atherosclerosis [16]. Angiogenic factors too are cardiocytoprotective [16]. VEGF acts in hypertension [29] with interleukin-6 by inducing arteriopathy. FGF also relates to hypertension [30]. HGF is notable in diabetic arteriopathy [31] and decreases plaque stability [32].

Conditions producing high levels of proinflammatory mediators—rheumatoid arthritis and periodontal disease—show ambiguous association with ischaemic cardiac disease [33,34]. The reasoning for this may rest on competition between cardiocytoprotection *versus* vascular damage. This may explain why erythropoietin [1–3] appears of questionable clinical value for AMI management [35]. Inflammatory factors impact more on cardiac and vascular remodeling/fibrosis/hypertrophic changes than ischaemic change [36,37], predictably leading to cardiomyopathy and explaining the resultant hypertension in periodontal disease and rheumatoid arthritis [38,39].

Partitioning the cardiac from the vascular system may provide mechanistic support for clinical observations in chronic inflammatory disease and for risk stratification. Ischaemic heart disease which presents with nil detectable CAD [40] has an improved prognosis. Doubtlessly, a significant percentage of the population may have underdiagnosed CAD with nil ischaemic change—raising the notion of intrinsic cardioprotection. Caution must be employed with anabolic androgen use as although such compounds are vasculature protective [41], they endanger the myocardium [42]. My proposition here is to explain that the heart and vessels—although clearly linked—represent differing substrates to an array of prosurvival and inflammatory factors—‘*two faces of the one coin*’. This partition is not a true dichotomy, which is an oversimplification, since mechanisms are shared: prosurvival leading to vascular smooth muscle proliferation and cardiac

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Fig. 1 *Two sides of the one coin*: Dual prosurvival and proinflammatory mediators act on two differing substrates of the one system—the cardiac and vascular system—maintaining homeostasis across the partition (horizontal arrow). In the heart, cardiocytoprotection to redox challenge is met by these factors yet in the vascular system, such mediators may adversely result in atheroma and reactive vascular smooth muscle hypertrophic alteration (hypertension). A finely-tuned ‘balancing-act’ exists within both the heart and vascular system (vertical arrows). In this respect, either ‘side of the coin’ share a commonality. Dual acting mediators in the heart may promote inflammatory-related fibrosis, adverse remodeling, cardiomyopathy and heart failure yet, equally, on the ‘other side of the coin’, such factors (for example: NF- κ B, TNF, endothelin, HIF, sphingosine-1-phosphate, interleukin) may confer some degree of vascular cytoprotection

hypertrophic change [4,43,44] and inflammation resulting in adverse vascular and cardiac outcomes (Fig. 1).

My ‘take home message’ for clinicians is that the cardiac and vascular system represent parts of one whole. Maintaining homeostasis between these parts is key in management and understanding the relation of chronic inflammatory diseases to cardiac and vascular health.

Conflict of interest The author declares no conflict of interest.

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