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INVITED EDITORIAL

Impairment of Vascular Homeostasis in Acute Heart Failure: Enter the Monocyte?

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Acute Heart Failure: Beyond the Starling Equation

The major function of the systemic circulation is the delivery of oxygen, nutrients, and circulating hormones such as nitric oxide (NO) to the tissues, together with reciprocal return of tissue metabolites, notably carbon dioxide, to the pulmonary vascular bed for clearance from the body. In 1896, Ernest Starling proposed an equation to summarise the interactions between hydrostatic and tissue oncotic forces which govern exchange of fluid within the peripheral microcirculation [1]. This equation of control of peripheral vascular homeostasis of fluid balance proposed high filtration rates outwards within the arteriolar side of the peripheral circulation, with similar return of fluid on the venular side. This equation has had a longstanding and profound effect on clinical interpretation of circulatory physiology, with the corollary that development of peripheral oedema reflects either increases in venular pressure and/or decreases in oncotic pressure of venous blood. Clinically, the concepts inherent in the original Starling equation are consonant with the gradual development both of peripheral oedema and of pulmonary congestion: for example, plasma albumin concentrations may decrease gradually, or pulmonary venous pressures may rise as a result of impairment of left ventricular relaxation and/or of mitral valve regurgitation. However, in many cases, pulmonary oedema develops suddenly, often in the face of chronic impairment of left ventricular systolic and diastolic function, and not necessarily in association with any acute decline in that function. This common clinical scenario is superficially at odds with the original version of the Starling equation and is most consistent with the occurrences of transient increases in microvascular permeability [2].

The questions therefore arise: (i) Is it possible that acute heart failure (AHF; for example, with associated development of pulmonary oedema) might be engendered primarily by changes in microvascular permeability? And (ii) What are the mechanisms whereby postulated acute changes in microvascular permeability might occur?

The Endothelial Glycocalyx: 'Gatekeeper' for Endothelial Function and Permeability

Even in an era when 'endothelial dysfunction' is a verbal knee-jerk term for the pathogenesis of many vascular disease states, relatively few clinicians are aware of the existence or pivotal physiological roles of the vascular endothelial glycocalyx (eGC), which is a mesh of negatively charged, endothelium-bound glycoproteins, proteoglycans, and glycosaminoglycans located on the luminal surface of vascular endothelial cells. The eGC has a constantly changing composition, probably representing 'fine tuning' if its physiological roles. Among the major structural components of the eGC are the syndecans, heparan sulphate, and hyaluronic acid [3].

The eGC exerts a number of fundamental and critically important effects as regards the control of circulatory physiology, including modulation of vascular rheology and of vascular permeability [2, 3]. Thus, loss of structural integrity of the eGC (glycocalyx 'shedding' or 'erosion')

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is associated with increases in microvascular resistance, which are now recognised as major contributors to incremental vascular stiffness associated with normal ageing, hypertension, and diabetes mellitus, as well as increases in 'leakiness' of coronary and systemic microvessels. This increase in eGC permeability has led not only better understanding of the pathogenesis of acute pulmonary oedema and to revision of the classical Starling equation to take account of a variable endothelial barrier to fluid exchange [3, 4] but also to more focused evaluation of the pathogenesis of cellular infiltration of tissues with leukocytes and macrophages during inflammatory reactions [2–4]. For example, increased permeation of the eGC has been implicated in acute inflammatory extravasation of neutrophils, lymphocytes, and monocytes, with neutrophils also acting as modulators of damage to the eGC [5].

Interactions between eGC dysfunction and risk of *platelet aggregation* on vascular surfaces are also emerging as a critically important pathophysiological issue, related especially to acute coronary syndromes. In general, damage to the eGC is associated with increased platelet activation, aggregation, and fragmentation, as we have recently demonstrated during symptomatic crises in patients with coronary artery spasm [6]. On the other hand, there is increasing evidence that aggregating platelets both physically and pharmacologically tend to stabilise vascular permeability in circumstances of acute injury, via autacoidal release of agents increasing barrier function [5].

An important issue which currently awaits full clarification is the relationship between damage to the eGC and '*endothelial dysfunction*', normally (and loosely) not only interpreted as impairment of vasodilator effects dependent on endothelial-dependent nitric oxide (NO) generation and/or NO signalling but also related directly or via autacoidal interactions with the integrity of vasodilator effects of other endothelial autacoids such as prostacyclin, carbon monoxide, hydrogen sulphide, and angiotensin (1–7). Despite the limitation of available data, there is strong evidence that shear stress-induced NO production may be modulated substantially via integrity of the endothelial glycocalyx: furthermore, Yen et al. [7] demonstrated in rat mesenteric arterioles that glycocalyceal heparan sulphate plays a major role in transducing mechanosensing of high flow to increase NO synthase activation. A study by Bar et al. [8] in young APOE/LDL receptor knockout mice showed *pre-atheromatous co-development* of glycocalyceal damage and endothelial dysfunction but did not examine cause-effect relationships for these phenomena. These issues are now of pivotal pathogenetic significance, given that large coronary artery atherogenesis no longer can be seen to represent the major basis for coronary event risks [9].

Monocytes and Glycocalyx Damage in Acute Heart Failure: What Can We Learn from Grushko et al.?

The stimulus for this Editorial Comment was provided by the recent publication in Cardiovascular Drugs and Therapy of an original research report from Grushko et al. [10], delineating the results of experiments related to the potential role of monocyte activation as a *pivotal component* of the inflammatory response to AHF. In a group of patients hospitalised with AHF, compared with control subjects, they investigated the mechanisms whereby concomitant monocyte activation (classically triggered by liposaccharide (LPS)-Toll-like receptor 4 (TLR-4) interaction) occurs in such patients. Unfortunately, the clinical characteristics of the 17 AHF patients studied are not well-described; other than that, their mean left ventricular ejection fraction was 20%. The implication, therefore, is of the occurrence of *acute-on-chronic* heart failure, often with past histories of hypertension and/or of known ischaemic heart disease. In particular, we have no information as to the extent of hypoxia at presentation in these patients, which might have served as an indirect measure of the extent of fluid extravasation into the lungs. In a sense, these clinical data alter the interpretation of the results of the study, because it is already known that patients with severe chronic heart failure exhibit evidence of damage to the eGC [11]. Only 5 control subjects were studied, limiting the power of the study.

The initial finding was that plasma concentrations of the eGC component heparan sulphate were significantly greater in plasma of AHF patients than in that of control subjects. It is not at all clear why similar findings were not made for other eGC components (hyaluronan and syndecan-1). Although hyaluronan levels were not elevated, the levels in individual patients correlated directly and significantly with hsCRP concentrations, thus suggesting a nexus with extent of inflammatory activation.

More importantly, plasma concentrations of heparan sulphate were directly correlated with monocyte expression of CD14, a marker of monocyte activation. The authors therefore went on to investigate whether activation of monocytes from normal subjects (via exposure to LPS, a ligand of TLR4) also induced changes in the *monocyte* glycocalyx (mGC). Indeed, content of mGC was substantially reduced, suggesting that monocyte activation led to shedding of much of the mGC. The next question was whether these released fragments might in turn contribute to overall inflammation in AHF. Indeed, it was found that disruption of the mGC was associated with amplification of monocyte activation, triggering release of TNFα and of IL-6.

The results of this study therefore provide evidence that AHF is associated not only with eGC damage but also

with monocyte activation, which results in mGC damage (Fig. 1A–C). Furthermore, damage to the mGC creates a 'vicious cycle' effect, further increasing monocyte activation and monocyte production of inflammatory cytokines (Fig. 1C). The overall associated pathophysiological consequences of these processes are schematized in Fig. 2.

What remains to be elucidated at this stage? First, we need to know more about the extent of individual versus coordinated overall control of the various components

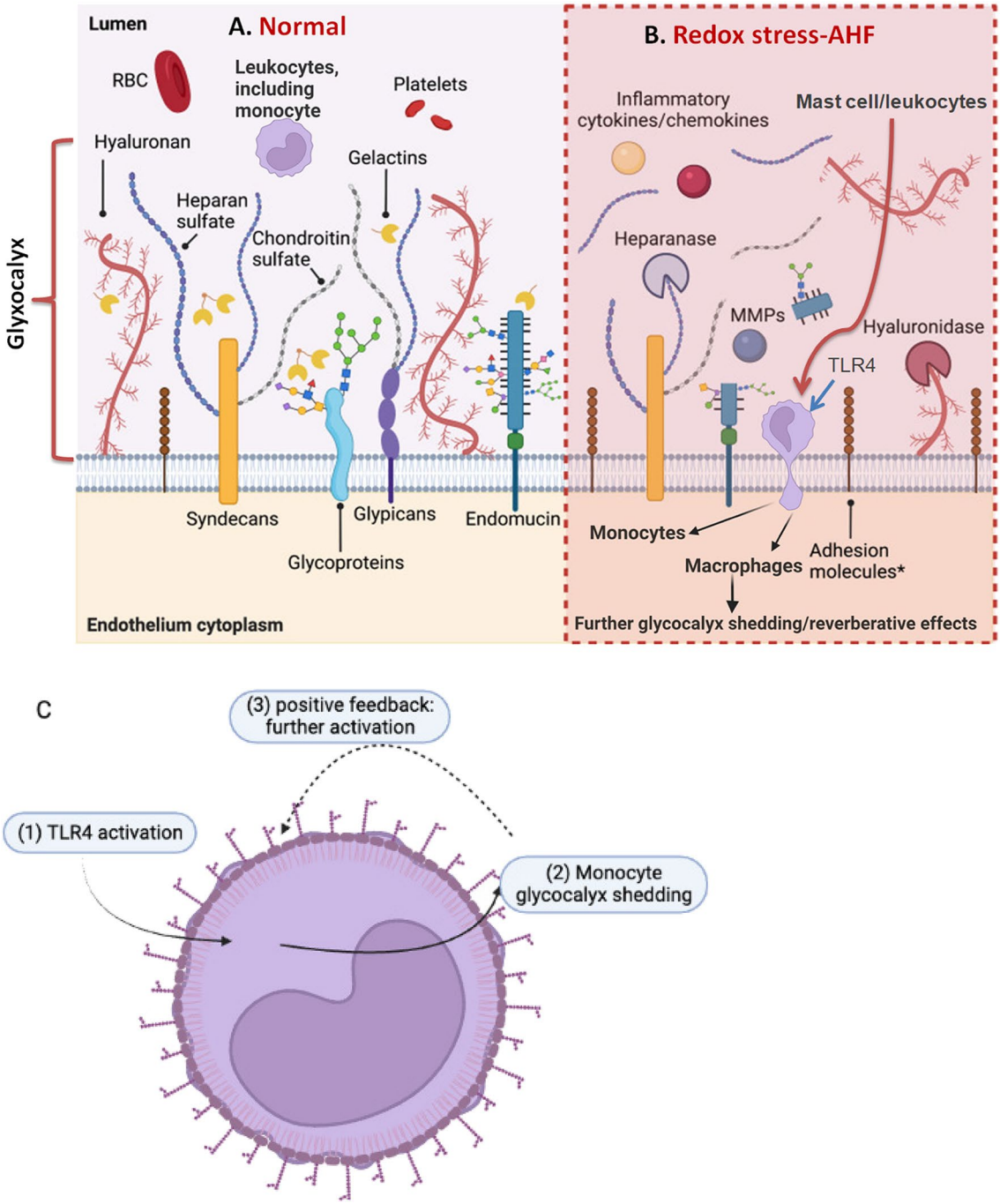

Fig. 1 Schematic representation of changes within vascular lumen/endothelial glycocalyx and endothelium occurring under redox stress, as associated with acute heart failure (AHF). **A** Note constituents of normal endothelial glycocalyx. **B** Note (1) enzymes cleaving glycocalyx components (heparanase, matrix metalloproteinases (MMPs), hyaluronidase). (2) Monocyte activation and permeation of glycocalyx by Toll-like receptor 4 (TLR4) in the presence of redox stress. Because of resultant glycocalyx permeation, monocytes penetrate endothelial cells with partial differentiation into macrophages. **C** Details of changes at level of monocyte including positive feedback

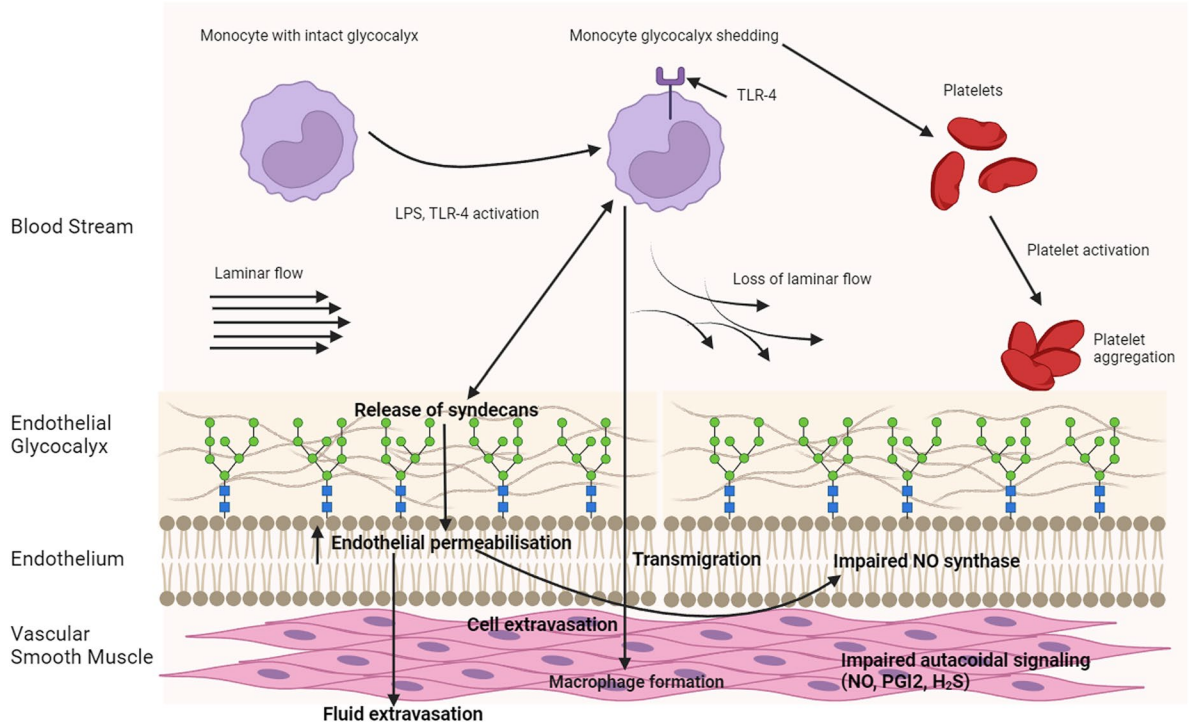

Fig. 2 Schematic view of changes at levels of vascular lumen, eGC, endothelial cells, and within vascular smooth muscle, in association with redox stress. Note. Contribution of monocyte glycocalyx shedding to overall process

of glycocalyx shedding associated with acute inflammatory states, which include not only heart failure (acute and chronic) but also acute myocardial ischaemia due to acute myocardial infarction [12] or acute exacerbations of coronary artery spasm [6]. Perhaps of greatest interest, TakoTsubo Syndrome, which usually presents as an acute coronary syndrome and evolves into a prolonged myocarditis-like condition with associated myocardial infiltration by neutrophils and macrophages, is associated with marked release of syndecan-1 into plasma, indicative of eGC 'shedding' [13]. Furthermore, eGC 'shedding' has been extensively documented in association with sepsis and the acute phase of COVID-19 infection. In none of these conditions has the question of how the better-known phenomenon of eGC damage might interact directly rather than indirectly with activation and transmigration of neutrophils and monocytes, or indeed with the pro-inflammatory effects of the resultant accumulation of tissue macrophages. Together, Figs. 1 and 2 schematize our current understanding of this complex process of circulatory disturbance through impaired microvascular rheology, vascular permeabilization with efflux of not only fluid but also of inflammatory cells, and platelet activation/adhesion/aggregation [5].

It is also more apparent than ever that the (patho)physiological roles of activated monocytes *per se* need to be considered, rather than simply considering monocyte activation as a precursor to conversion to macrophages with a spectrum ranging from pro- to anti-inflammatory properties.

How Might This Be Important Therapeutically?

As summarised above, many of the pathophysiological (fluid extravasation, tissue inflammation, microvascular constriction) and pharmacological (loss of responses to nitric oxide) aspects of coronary microvascular dysfunction and of associated platelet aggregation have been attributed primarily to 'shedding' of eGC. It is clear from the recent work of Grushko et al. [10] that monocyte activation and mGC shedding also contribute to these processes.

Whether this be of importance in the management of acute or chronic oedema where management has previously centred on intravenous administration of loop diuretics? It has previously been demonstrated that parenteral administration of organic nitrates, either alone [14] or together with the antioxidant/hydrogen sulphide donor N-acetylcysteine [15], is at least equi-effective with diuretic-based treatment in reversing hypoxia in this circumstance. Specifically directed trials of eGC and mGC stabilisation, for example, with matrix metalloproteinases inhibitors, now represent, at least in theory, an attractive alternative.

Table 1 Potential therapeutic avenues: eGC 'shedding'

Strategy	Mediators
Mast cell stabilisation (limits 'sheddase' release)	Autacoids: NO, H_2S Corticosteroids: hydrocortisone Leukotriene antagonists Antihistamines Mast cell stabilisers (e.g. sodium cromoglicate and ketotifen)
Inhibition of 'sheddases'	Doxycycline, berberine, S1P, sulphated tyrosine, angiopoietin-1, SOD, sevoflurane, and sulodexide
eGC reconstituents	Dextran sulphate, albumin, and H_2S

Potential strategies for either direct or indirect stabilisation of eGC and mGC in the face of redox stress are summarised in Table 1.

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Declarations

Competing Interest The authors have no relevant competing interests.

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