Editorial Focus

Cell-derived microparticles: A mediator of inflammation in aortic valve stenosis?

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Aortic valve stenosis (AVS) is quite common, affecting some 30% of those over age 65 (1). It frequently progresses to severe obstruction necessitating surgical repair or replacement of the stenotic valve. Annually more than 50,000 aortic valves are replaced surgically in the USA, posing common and serious medical problems (2), yet our knowledge of the pathogenesis and optimal treatment of this condition is surprisingly limited. It may represent a manifestation of atherosclerosis affecting the endothelium lining the heart valve but this is still debated. There is mounting evidence that AVS is associated with systemic inflammation (3, 4). Some but not all studies found an association of AVS with elevated C-reactive protein (CRP) (3) and active atheroinflammatory processes (4), implying a role of inflammation in the pathogenesis of AVS.

Even if true, however, there is little insight on exactly how or why mechanical perturbation of blood flow due to AVS leads to systemic inflammation, or what inflammatory processes promote the initiation and progression of AVS. Elucidation of this key issue could provide a rational basis for prevention and therapeutic strategies.

The intriguing report by Diehl et al. in this issue of *Thrombosis and Haemostasis* (5) may offer an insight into this problem, and may be of potential clinical importance. They hypothesize that AVS induces generation of circulating cell-derived microparticles (MP) by shear stress, and that the resulting MP then promote systemic inflammation. Briefly, their scenario goes like this: high shear stress generates platelet microparticles (PMP), which in turn interact with leukocytes to activate them and elicit release of leukocyte MP (LMP) and monocyte MP (MoMP). These procoagulant and inflammatory MP, along with activated monocytes, can induce endothelial injury at the lining of the heart valve, thereby setting up a "vicious cycle," as the authors put it, leading to further calcific stenosis of aortic valves as seen in AVS. Endothelial cell injury is reflected by release of endothelial MP (EMP) (6).

This hypothesis is novel and intuitively appealing. To support it, they measured MP species including PMP, LMP, and EMP in 22 AVS patients, and report a significant increase in all of them relative to controls. In parallel, elevation of markers of systemic inflammation was observed, such as soluble P-selectin, interleukin-6, and activation of monocytes. These data convincingly support the hypothesis, although falling short of conclusively establishing a cause-effect relationship between MP-cell interaction and progression of AVS.

In addition, since this is a cross-sectional study, more definitive support for an active role of MP in the pathogenesis of AVS will require a prospective longitudinal study correlating MP-cell interaction with progression of AVS, as the authors acknowledge in their discussion.

Thus, a central theme of this paper is the physiological relevance of MP-cell interactions. They demonstrate copious production of PMP in AVS, and correlation of PMP levels with valvular shear stress *in vivo*. Others have previously shown *in vitro* that PMP are readily generated by abnormally high shearing forces (7–9). It has also been shown that PMP can induce leukocyte activation (10, 11), and can act directly on endothelial cells (8, 12). High shear can also induce endothelial activation and release of EMP (13); and in turn, EMP can activate leukocytes (14–17). Indeed, EMP were reported to act on the endothelial cells that produce them (18). Mixed MP isolated from patients were shown to be deleterious on cells *in vitro* or *ex vivo* (19, 20). Finally, the LMP elicited by PMP or other MP are known to be injurious to endothelial cells (21, 22).

In view of these and other reports cited by Diehl et al. (5), there is ample evidence *in vitro* to support their hypothesis, that interactions of shear-generated MP with blood cells and endothelium could be pivotal in the progression of AVS.

Their report struck a chord with us because of our anecdotal observation some years back of a patient with severe AVS, who refused surgical intervention. Her PMP counts were among the highest we had ever seen. She suffered from numerous recurrent transient ischemic attacks, progressing to advanced dementia. Thus, it is gratifying to see our observation confirmed in a significant number of patients by the work by Diehl et al.

What implications might this report have for therapeutic strategies? If the hypothesis of Diehl et al. reported in this issue is correct, then it may be time to begin thinking about ways to modulate MP-mediated injury. Two approaches come to mind,

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first being to inhibit their interaction with cells, the second being to inhibit MP release. Regarding the first, several strategies are now being tried or considered which block specific cell-cell adhesion molecules, such as P-selectin and ICAM-1 in coronary disease (23, 24), or VLA-4 in inflammatory bowel disease, multiple sclerosis, and Crohn's disease (25, 26). Since many of the same adhesins are involved with MP-cell interaction, this might be a fruitful approach.

The other possible approach is to specifically inhibit the release of MP from their parent cells. Several such inhibitors are known, such as calpain inhibitors, but whether they are suitable for therapeutic purposes *in vivo* is not clear. The biochemical pathways underlying MP release have recently been elucidated by Flaumenhaft et al. (27, 28), and indicate that PIP2 could possibly be a useful therapeutic agent. Other inhibitors were explored by Abid-Hussein et al. (29). However, to our knowledge, none of these agents has yet been tested for efficacy or toxicity *in vivo*.

Currently, therapies to prevent progression of AVS receive increasing attention (2). Among them, statins have shown promise in some studies (30) but not in another (31). The outcome of large trials now in progress is awaited (31). However, it is of interest to note that Tramontano et al. reported that statins effectively inhibit the release of EMP from endothelial cells (32). The putative benefit of statins for AVS may derive in part from inhibition of MP release.

Cell-derived MP are no longer esoteric curiosities, as evidence mounts for their significance in disorders ranging from thrombosis, atherosclerosis, and inflammation to cancers. For example, MP carrying tissue factor are associated with thrombosis in cancers (33–35), and we have recently demonstrated that plasma MP, not the soluble components of plasma, are responsible for the elevated thrombin generation of plasma from patients with thrombosis (36). Dozens of other reports now implicate MP in a wide variety of disorders, including neurological diseases (37).

Whatever the final disposition vis-a-vis therapy for the complex disorder of AVS (30, 38, 39), the study of Diehl et al. surely stands as a further indication of how MP analysis can often supply novel and potentially fruitful explanations for the progression of inflammatory and thrombotic disorders.

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