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Review

Revisiting cardiovascular calcification: A multifaceted disease requiring a multidisciplinary approach

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ABSTRACT

The presence of cardiovascular calcification significantly predicts patients' morbidity and mortality. Calcific mineral deposition within the soft cardiovascular tissues disrupts the normal biomechanical function of these tissues, leading to complications such as heart failure, myocardial infarction, and stroke. The realization that calcification results from active cellular processes offers hope that therapeutic intervention may prevent or reverse the disease. To this point, however, no clinically viable therapies have emerged. This may be due to the lack of certainty that remains in the mechanisms by which mineral is deposited in cardiovascular tissues. Gaining new insight into this process requires a multidisciplinary approach. The pathological changes in cell phenotype that lead to the physicochemical deposition of mineral and the resultant effects on tissue biomechanics must all be considered when designing strategies to treat cardiovascular calcification. In this review, we overview the current cardiovascular calcification paradigm and discuss emerging techniques that are providing new insight into the mechanisms of ectopic calcification.

Contents

1. Introduction

Clinical evidence demonstrates that calcium burden significantly predicts and contributes to cardiovascular disease [1–3], the leading cause of death in the United States. However, no known therapeutic strategies exist to prevent or treat cardiovascular calcification. Previous studies have focused on the cellular

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and molecular changes that drive soft tissue calcification while the physicochemical processes by which mineral forms and grows remain unknown. Cardiovascular calcification lies at the interface of physical, chemical, and biological fields, requiring a multidisciplinary approach to connect the cellular and molecular changes to the remodeling that disrupts tissue function. Pathologic changes in cell phenotype (biological) create an environment favoring calcium phosphate mineralization (chemical), leading to loss in the biomechanical function of the soft tissue (physical). Understanding the integration of these processes requires a multidisciplinary approach with the common goal to develop new therapeutic strategies to control ectopic biomineralization. In this review, we provide a holistic discussion of cardiovascular calcification connecting the tissue alterations to the disease cellular underpinnings. Section 2 overviews the biomechanical changes that result in the clinical manifestation of calcification. Recent material and chemical analyses of cardiovascular calcification are reviewed in Section 3. In Section 4 we introduce the cellular populations and phenotypes responsible for mineral deposition. Finally, we discuss the commonly used methods exploring molecular mechanisms of calcification along with the emerging technologies offering novel mechanistic insight.

2. Cardiovascular calcification and tissue biomechanics

2.1. Introduction

Cardiovascular tissues function in a dynamic environment. Over the course of the cardiac cycle, cardiovascular tissues expand and contract ensuring proper blood distribution throughout the body. Appropriate biomechanical properties of these tissues depend upon the microarchitecture of the extracellular matrix [4]. Calcification disrupts this microarchitecture through the deposition of hard mineral within the soft tissues [5]. The resultant loss in biomechanical integrity can lead to both chronic and acute deleterious effects [5–7]. Specifically, two types of cardiovascular calcification significantly impair human health: arterial microcalcification and aortic valve macrocalcification [8,9].

2.2. Arterial calcification

Prospective clinical data show that the risk of cardiovascular events inversely correlates with the density of calcification present within arterial plaques as measured using computed tomography [10]. It is now well-accepted that the presence of "spotty" calcification is associated with increased cardiovascular morbidity [10,11]; however, the potential causality relationship between calcification morphology and cardiovascular risk was not made clear by clinical and histopathological studies. Recent work using finite element modeling of stress distribution within atherosclerotic plaques indicates that subcellular microcalcifications in an atherosclerotic fibrous cap promote material failure of the plaque [12–14], causing myocardial infarction and stroke. The atherosclerotic fibrous cap serves as the main barrier between the pro-inflammatory lipid pool within the plaque and the blood flowing through the arterial lumen. When this cap ruptures, platelets rapidly accumulate to form a fibrin clot during a process known as thrombosis. Local occlusion of the vessel by these thrombotic clots causes 60% of all myocardial infarction [15,16].

Each time the heart pumps during systole, increased pressure leads to expansion of the arteries, generating stresses within the fibrous cap. Plaque rupture occurs when this stress reaches a critical threshold where the collagen fiber network of the fibrous cap, can no longer remain intact [17]. Classically, weakening of the fibrous cap has been attributed to inflammation-dependent proteolytic degradation of collagen [18]. As collagen diminishes, the fibrous cap network becomes thinner and more likely to rupture under stress. Using material-based theories and knowledge of the properties of collagen, computational (*i.e.*, *in silico*) models can predict fibrous cap stresses and the critical stress required for rupture [7]. These finite element analyses predict the stress by segmenting a plaque into discrete nodes. The stress at each node is calculated based upon the known material properties of the plaque constituents and the local geometry (*e.g.*, curvature) at the node. By increasing the number of nodes at which these calculations are performed, the localized stresses throughout the plaque can be estimated [17]. Predictions based on modeling a homogenous collagen network in the fibrous cap suggest that plaque rupture should occur when the cap is less than approximately 65 μm thick [19–21], and rupture should primarily occur at the shoulders of the plaque [22]. Histopathological observations, however, indicate that 37% of cap ruptures occur at the center of the plaque, and ruptures in caps as thick as 160 μm have been observed [23]. Inclusion of microcalcifications in fibrous cap models, predicts rupture criteria closely match the histopathological observations [24–26]. Rigid microcalcifications do not stretch, as such fibrous cap collagen deforms around microcalcifications, amplifying stress, and increasing cap rupture risk (Fig. 1). Model data suggest that plaque rupture is a function of both fibrous cap thickness and the presence, size and orientation of microcalcifications embedded within the cap [12–14,27,28]. These findings corroborate the clinical data that demonstrate an inverse relationship between calcification density and cardiovascular events [11]. High resolution micro-computed tomography imaging identified a preponderance of small microcalcifications scattered throughout excised human coronary arteries [14]. In contrast to the increased cap stress caused by microcalcifications, large, dense calcifications may stabilize the plaque [17,29–31], although the mechanisms giving rise to these different calcification morphologies are unclear. Once an atherosclerotic plaque develops, a therapeutic goal could be a treatment tilted toward an increased fibrocalcific response. As discussed in Section 2.3, a heightened fibrocalcific response, however, must be avoided in the context of the other major site of cardiovascular calcification: the aortic valve.

It should be noted that the discussion to this point has considered atherosclerotic calcification only. Atherosclerosis manifests as localized plaques at specific arterial positions [32]. Therefore, increased fibrocalcific remodeling at these locations do not appreciably compromise the integrity of the vasculature [33]. In contrast, conditions leading to elevated serum phosphate (*i.e.*, hyperphosphatemia), in patients undergoing dialysis for chronic renal disease, lead to gross medial calcification that can severely alter arterial elasticity [34]. It is likely that in these patients, the most appropriate therapeutic goal would be prevention of the initial mineral deposition.

2.3. Calcific aortic valve disease

The aortic valve is situated between the left ventricle and the aorta and controls unidirectional blood flow from the heart to systemic circulation. Unlike most other cardiovascular tissues, the motion of the aortic valve is determined predominantly by cardiac pressure and hemodynamics. An excellent review of the structure-function relationship is provided by Sacks et al. [4]. Here, we offer a short summary of aortic valve physiology to emphasize the impact of calcification on valve function. Three thin membranous leaflets at the base of the valve recoil toward the aortic wall during systolic contraction of the ventricles, allowing blood to be pushed from the heart into the aorta. As the heart rests in diastole, the reversed pressure gradient forces these leaflets to stretch toward the center of the aortic annulus (Fig. 2A). As they stretch, adjacent leaflets meet and seal the valve orifice, preventing retrograde blood flow into the