Cardiovascular Pathology 22 (2013) 1–8

Contents lists available at SciVerse ScienceDirect

Cardiovascular Pathology

Review Article

The progression of calcific aortic valve disease through injury, cell dysfunction, and disruptive biologic and physical force feedback loops

Chen Li [1], Songyi Xu [1], Avrum I. Gotlieb *,[2]

Laboratory Medicine Program, Toronto General Research Institute, University Health Network, Ontario Canada M5G 1L5
Department of Laboratory Medicine and Pathobiology, University of Toronto, Canada M5G 1L5

ARTICLE INFO

Article history:
Received 28 April 2012
Received in revised form 1 June 2012
Accepted 4 June 2012

Keywords:
Calcific aortic valve disease
Valve interstitial cell
Matrix remodeling
Physical forces

ABSTRACT

Calcific aortic valve disease (CAVD) is the most common form of heart valve disease in Western society and results in the second most common cardiovascular surgery performed. Despite its prevalence, high morbidity, and high mortality, the pathogenesis of CAVD still eludes our understanding. This review article brings together experimental in vivo and in vitro as well as human in vivo research in cell and molecular pathobiology to construct an overarching hypothesis regarding the development and progression of CAVD. We focus on injury, cell dysfunction, and disruptive biologic and physical forces, and how they function in positive feedback loops that result in the eventual calcification of the valve. We propose that injury, inflammation, matrix remodeling, and physical forces are all processes that influence each other and alter the normal physiologic functions of a key player in the pathogenesis of CAVD: the valve interstitial cell. We propose that the different phenotypes of the valve interstitial cell play essential roles in the pathogenesis of CAVD. We describe important physiologic processes which become dysfunctional including proliferation, migration, secretion of growth factors, chemokines and cytokines, and matrix remodeling. We also describe the emergence of chondrogenesis and osteogenesis in the fibrotic valve that lead to the severe clinical conditions of CAVD. CAVD appears to have a complex pathogenesis which fortunately can be studied in vitro and in vivo to identify ways to detect, treat, and prevent CAVD.

1. The human aortic heart valve

The valves of the human heart are fascinating biological structures that are associated with flowing blood and mechanical forces and whose function depends on the complex interaction of cells, matrix, and physical forces. They regulate blood flow inside a complex multichambered pump. The valve cusps of the aortic valve are attached at the base of the aortic outflow tract. The highly organized extracellular matrix (ECM) of valves serves to maintain physiologic structure and, together with a heterogeneous population of constituent cellular elements, regulate complex functions to give both flexibility and durability to the cusps [1,2]. The four types of cells found in valves are surface valve endothelial cells (VECs), valve interstitial cells (VICs), and, towards the base of the valve, cardiac muscle cells and smooth muscle cells. A confluent monolayer of VECs lines the surface of the valve. VECs show regional characteristics as differences in gene expression have been identified when comparing VECs on the fibrosa to those on the ventricularis side of the aortic cusp [3]. Beneath the endocardium, VICs are embedded in matrix which VICs themselves secrete and which in turn plays a role in regulating cellular function [1]. The matrix is distributed in the three histologically distinct layers of the valve: the fibrosa on the sinus side, the spongiosa in the middle, and the ventricularis on the aortic outflow side [4,5]. The fibrosa is rich in densely packed collagen fibers aligned along the circumferential direction of the cusp; the spongiosa is composed mainly of glycosaminoglycans (GAGs) and proteoglycans; and the ventricularis contains prominent elastin with collagen, GAGs, and proteoglycans [6]. These layers provide the valve with a zone of stiffness giving rise to a load-bearing structure of the cusp, a zone which is compressible and dampens compressive forces during diastolic filling, and a zone which is elastic in nature, respectively. The fibrosa with its dense connective tissue provides strength when the valve is shut, the spongiosa with its loose matrix of glycoproteins provides a cushion and a lubricating layer for the physical forces when the valve opens and shuts, and the ventricularis provides elasticity through elastin fibers that are mainly oriented in the radial direction. When the cusp changes shape during the cardiac cycle, the collagen fibers return to their original orientation after the mechanical load has been released through the elastin fibers in the ventricularis. All three layers are avascular, and the distinct layers are formed at least in part by the physical forces which are applied to the valve by hemodynamic

* Corresponding author. Faculty of Medicine, Medical Sciences Building, 1 King's College Circle, Rm. 2115, Toronto, Ontario M5S 1A8 Canada. Tel.: +1 416 978 4635; fax: +1 416 946 5963.
E-mail address: avrum.gotlieb@utoronto.ca (A.I. Gotlieb).
[1] Equal participation as first authors.
[2] Dr. Gotlieb is the recipient of the 2012 SCVP Distinguished Achievement Award.

1054-8807/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
doi:10.1016/j.carpath.2012.06.005

sheer stress and mechanical forces. This was shown by a study of human valves. In the embryonic stage (up to 20 weeks), there are no layers present, and then two layers appear. The trilaminar architectural pattern occurs after birth during the time that blood flow patterns are established postnatally [7]. This exquisite architecture is the result of a specific organization of cells and matrix which may then function for decades and decades with minimal tissue wear and free of clinical disease. Although the cellular and molecular mechanisms that regulate the formation of the trilaminar compartmentalization are unknown, they merit intense study since it is likely that even mild disruption of the architecture may promote mild valve dysfunction which in some individuals progresses toward clinical disease.

2. Clinical features of calcific aortic valve disease (CAVD)

2.1. Clinical presentation

CAVD, commonly also referred to as calcific aortic stenosis, is the most common heart valve condition in adults in Western society and results in the second most common cardiovascular surgery performed [8]. At present, the pathogenesis of CAVD is unknown; however, similar calcific aortic valve conditions occur in some cases of bicuspid aortic valves, usually appearing clinically in the 40- and 50-year age range, about 10 to 20 years before CAVD presents clinically. CAVD is a disease with high morbidity and mortality that is costly to the health care system and will become even more prominent in health economies as people live longer. It has precursor lesions that may remain asymptomatic for some time [9]. During the precursor stage of the disease, aortic valve sclerosis occurs, which results in cusp thickening without creating obstruction to the left ventricular outflow [9]. CAVD may be considered to have a silent phase, which may provide opportunities for therapeutic intervention to prevent or at least slow down the progress of disease. With onset of clinical disease, obstruction to left ventricular outflow occurs. Left ventricular hypertrophy, angina, cardiac arrhythmias, dizziness, syncope, and congestive heart failure occur over time. CAVD increases in prevalence with advancing age. While 20%–30% of individuals over the age of 65 and 48% of individuals over 85 are affected by valve sclerosis, only 2% of individuals over 65 and 4% of individuals over 85 end up with CAVD [8,10]. What leads to this progression from aortic sclerosis to CAVD is unknown; however, it is likely that environmental and genetic factors play a role. The key to understanding progression may be in a faulty valve repair system present in some individuals. In these cases, instead of remodeling and repair to a normal or near-normal physiologic state, there is excessive valve thickening due to sclerosis that promotes valve dysfunction. Valve cusp stiffening leads to alterations of hemodynamic shear stress and mechanical stress in the valve which then leads to more biochemical cell dysfunction and sclerosis, and thus, a vicious positive loop occurs, leading to eventual clinical disease. These disruptive biologic and physical force feedback loops need to be understood to design therapeutic approaches to block them effectively. Risk factors have been identified and include hypertension, elevated low-density lipoprotein (LDL), male gender, smoking, and diabetes mellitus, which are similar to those of atherosclerosis [11]. Statins, well-known therapeutic agents that effectively target atherosclerosis, have been shown to be ineffective in a few prospective clinical trials on more advanced CAVD [12–14]. It is still possible that future studies designed to treat CAVD patients very early on will show a benefit in slowing down the progression of CAVD. The mainstay of treatment for CAVD is still surgical valve replacement, which results in a dramatic improvement of symptoms [15]. The procedure is costly and carries a certain amount of risk. In populations with access to cardiovascular surgery, over 285,000 patients undergo replacement worldwide annually, but 60% suffer from valve-related complications by 10 years after surgery [16]. Transcatheter aortic valve implantation is a relatively new technique first done in humans in 2002. It is gaining acceptance in patients unsuitable for conventional open-heart surgery, generally older patients over 70 years of age with severe CAVD [17].

2.2. Histopathology

The gross and microscopic features of human CAVD have been very well described in the cardiovascular literature [18]. Detailed histopathological investigations by anatomic pathologists have characterized the microscopic features of CAVD including changes in the number of VICs, accumulation of dense connective tissue matrix and myxomatous changes, inflammation with or without immune activity, neovascularization, necrosis, lipid deposition, calcification, and bone formation [18]. The morphology of calcification suggested a degenerative dystrophic process leading to passive accumulation of hydroxyapatite crystals in dead cells and surrounding tissue. The trilaminar architecture is disrupted. There are macrophages, foam cells, and T lymphocytes present in CAVD. Microthrombi may also be present on the surface of the cusps. The histologic features suggested tissue degeneration; so the condition was often referred to as degenerative valvular aortic stenosis. As our understanding of pathogenesis evolves, this term degenerative is falling out of favor to be replaced by active cell dysfunction.

3. Pathogenesis of CAVD

The early histopathology studies on human valves focused on degenerative processes. The more recent cell and molecular biology studies have linked structure and function, and their findings support active cell-based processes that regulate pathogenesis. In addition, experimental models of CAVD in rabbits [13] and mice [19–21], although not perfect models, should be able to further the structure function approach to understanding pathogenesis.

The alterations of tissue architecture and content are due to active cellular processes that, taken together, suggest that a “response to tissue injury” regulated by VICs is occurring in the valve [22–24]. The core processes that result in valve disease are part of the universal tissue repair processes present in human tissue and organs. Also, CAVD may be due to the reactivation of developmental programs that, in the adult, lead to valve calcification [25–27]. These two concepts are not mutually exclusive and do overlap. VICs, the most prevalent cells in the valve, become activated in response to injury. In diseased valves, they differentiate into myofibroblast type cells, expressing the marker alpha-smooth muscle actin (α-SMA) [28]. These activated VICs likely play a key role in the pathogenesis of human clinical disease when the “response to tissue injury” becomes excessive and leads to disruption of the cusps with excessive remodeling, scarring, and calcification through unknown mechanisms [22,24,29]. Thus, CAVD is no longer considered to occur due to passive degeneration secondary to aging. Research has shown that the pathogenesis involves active cell and tissue processes that occur as a tissue response to injury including inflammation, neovascularization, oxidative stress, activation of the renin–angiotensin system, matrix remodeling, and calcification and osteogenesis [24]. These processes develop as the valve cusps thicken due to fibrosis. Irregular calcified nodules develop initially at sites exposed to high mechanical force in the fibrosa layer of the valve.

An elusive issue is the identification of the tissue/cell injurious factors. It is likely that they will turn out to be bioactive agents, e.g., oxidized lipoproteins; environmental toxins, e.g., chemicals derived from cigarette smoking; microbial and viral agents; and abnormal hemodynamic and physical forces due to minor or major valve misalignments leading to endothelial injury and chronic tissue stress. It is likely that heterogeneous forms of injury either alone or in combination initiate and maintain a state of low-grade chronic injury.