Thank you for downloading this document from the RMIT Research Repository.

The RMIT Research Repository is an open access database showcasing the research outputs of RMIT University researchers.


Citation:

See this record in the RMIT Research Repository at:

Version: Accepted Manuscript

Copyright Statement: © 2008 Bentham Science Publishers

Link to Published Version:
http://dx.doi.org/10.2174/157340208784245884

PLEASE DO NOT REMOVE THIS PAGE
Calcific aortic valve disease and hypertension

Harsha Dadlani¹, Narin Osman¹,² Mandy L. Ballinger¹,
Silvana Marasco³ and Peter J. Little¹,²,⁴

¹Cell Biology of Diabetes Laboratory, Baker Heart Research Institute, Melbourne, Victoria, 3004, Australia
²Department of Immunology, Central and Eastern Clinical School, Alfred Hospital, Monash University, Melbourne, 3004, Victoria, Australia
³Department of Cardiothoracic Surgery, Alfred Hospital, Melbourne, Victoria 3004, Australia
⁴Department of Medicine, Central and Eastern Clinical School, Alfred Hospital, Monash University, Melbourne, 3004, Victoria, Australia

Address for correspondence:
Peter J. Little, Ph. D.
Cell Biology of Diabetes Laboratory
Baker Heart Research Institute
St. Kilda Rd Central
PO Box 6492
Melbourne Victoria 8008
Australia
Tel: +61 3 8532 1203
Fax: +61 3 8532 1100
Email: peter.little@baker.edu.au

Running title: CAVD and hypertension

Key words: Calcific aortic valve disease, hypertension, atherosclerosis, angiotensin converting enzyme inhibitors
Abstract:

This review addresses the role of hypertension in precipitating Calcific aortic valve disease (CAVD) and the therapeutic potential of anti-hypertensive interventions to ameliorate CAVD. CAVD was originally considered to be a degenerative disease representing the “wear and tear” of the aortic valves. More recently both conceptually and experimentally, CAVD has come to be considered the result of an active disease process. Whilst, there are some common factors in the pathology and risk factors for atherosclerosis and CAVD there are also some distinct differences. Hypertension is an established risk factor for coronary artery disease and has been recognised as a risk factor for CAVD. Angiotensin converting enzyme inhibitors have been found to have beneficial effects in CAVD and as in atherosclerosis such effects may be due to the blood pressure lowering action but also to direct pleiotropic effects on the biochemical and cellular mechanisms of disease progression in the respective tissues. The very high prevalence of hypertension in the community coupled with an aging population, a risk factor associated with both hypertension and CAVD, infers that hypertension will be one of the predominant factors that increase the impact of CAVD on human health in the coming decades.
INTRODUCTION

Calcific aortic valve disease (CAVD) is a progressive condition which leads to significant symptomatology and death if untreated. The prevalence of CAVD is increasing because of our increasingly elderly population. Currently 2-5% of very elderly patients are diagnosed with CAVD [1, 2] which carries an 80% 5 year risk of progression to heart failure, valve replacement or death [3]. CAVD is also the second most common indication for cardiac surgery in the Western world [4].

Initially thought to be a degenerative disorder of aging, increasingly specific risk factors are being identified in association with CAVD. Age, male gender, hypertension and current smoking have all been found to be associated with CAVD in a large population cohort study. Correlations have also been found between CAVD and elevated levels of lipoprotein and low density lipoprotein cholesterol. Other identified risk factors are diabetes, and elevated body mass index [5] and end stage renal disease [6].

As stated above, CAVD was originally considered to be a degenerative disease representing the “wear and tear” of the hard working aortic valves [7]. More recently conceptually and experimentally CAVD has come to be considered the result of an active disease process with the implication that it may be amenable to therapeutic intervention [8, 9]. The major observations indicating that CAVD is an active disease process are the deposition of lipid in early lesions, specifically lipids associated with atherosclerosis, the presence of monocyte macrophages and other cells of the immune system [9], the presence and involvement of proteins associated with calcification [10] and the presence of the components of the Renin Angiotensin System (RAS) including angiotensin converting enzyme (ACE), angiotensin II (AII) and angiotensin receptors [9, 11]. CAVD has a catastrophic impact on the appearance
of the valve leaflets (Fig. 1). Current concepts suggest an analogy between the pathological mechanisms of atherosclerosis [8] and CAVD however only 50% of patients with severe aortic stenosis have appreciable coronary disease, so clearly some differences must be present in the aetiology [12]. There are some common factors as well as distinct differences in the pathology and risk factors for atherosclerosis and CAVD. In atherosclerosis, the arterial neo-intima is the location of the formation of atherosclerotic plaques whereas CAVD disease commences within the boundaries of the valve and ultimately forces an expansion of the valve tissue [13]. Also, angiotensin receptors are expressed in VSMCs in the wall of normal vessels [14] but are not expressed by aortic valve myofibroblasts (avMs) in normal aortic valves [8].

There are however common factors as well. There is a large amount of literature on the relationship between hypertension and cardiovascular disease but very little on the mechanisms through which hypertension accelerates atherosclerosis. There is also only a small amount of information on the association and underlying mechanisms linking CAVD and hypertension. Hypertension is a strong and well-established risk factor for coronary artery disease and has been recognised as a risk factor for CAVD. Multiple trials have demonstrated the benefits of blocking RAS in preventing atherosclerosis-related cardiovascular disease [15-17]. However, as in the case that the hyperglycaemia of diabetes is more than just elevated blood glucose [18], hypertension seems to be more than just elevated blood pressure [19]. Studies on the relationship of systolic blood pressure and atherosclerosis show that more than pressure per se is involved [19] and by analogy with the role of insulin resistance in diabetes, the stimulus for the hypertension is strongly implicated. The major stimulus is the RAS and manipulations of the RAS system have a direct impact of atherosclerotic lesion size [19]. Angiotensin converting enzyme (ACE) inhibitors
have been found to have beneficial effects, but not unequivocally, in CAVD. As in atherosclerosis, such beneficial effects in CAVD may be due to the anti-hypertensive action and also pleiotropic effects directly on the biochemical and cellular mechanisms of disease progression [20]. The very high prevalence of hypertension in the community [21] coupled with the aging of the population which is associated with both hypertension and CAVD, infers that hypertension will be one of the major underlying factors that increase the impact of CAVD on human health in coming decades. This review addresses the role of hypertension in precipitating CAVD and the potential for therapeutic benefit of anti-hypertensive interventions to ameliorate CAVD.
ANATOMY AND PATHOLOGY OF CAVD

The processes causing the initiation and progression of aortic valve disease have not been clearly identified. Aortic valves have three distinct anatomical layers. These layers commencing from the upper or aortic side of the leaflet are the fibrosa, the spongiosa and the ventricularis and these are comprise predominantly collagen, glycosaminoglycans and elastin, respectively (see Fig. 2A). Pathologically, there are similarities but distinct differences between CAVD and atherosclerosis. The most important similarity is the co-localization of lipids with the proteoglycans, biglycan and decorin, in early CAVD and atherosclerosis [22-24]. Extracellular matrix (ECM) changes are characteristic of both atherosclerotic vessels and diseased aortic valves. Lipid-rich lesions accumulate predominately on the aortic surface of the valve [9], the basement membrane/elastic lamina beneath these lesions appears to be damaged or absent. The collagenous fibrosa becomes thickened [9], partially due to the infiltration of lipids. Proteoglycans, specifically the chondroitin/dermatan sulfate proteoglycans, biglycan, decorin, and versican, show increased abundance in early through late aortic valve lesions and biglycan and decorin are co localized with apoE and apoB [22, 23] (Fig. 2B). A fundamental difference is the development of atherosclerosis in the neointima of coronary arteries whereas in aortic valve pathology the neo-intima does not have an anatomical equivalent [13]. Other differences between aortic valve disease and atherosclerosis are the deposition of lipid in the sub-endothelial fibrosa layer in aortic valves but not in deeper layers, and calcification instead of necrosis as a response to lipid trapped in the valvular tissue [23, 25, 26]. Lipids, oxidized lipids, lipoproteins (Low Density Lipoproteins (LDL) and Lipoprotein (a)), and cholesterol are present in lesions of human sclerotic and stenotic
aortic valves, as well as in underlying regions of collagenous fibrosa [8, 9, 26, 27] characterized by elastic lamina fragmentation, macrophages, and accumulation of glycosaminoglycans (GAG) and proteoglycans [22, 23, 27].

Some signaling studies have provided evidence on the pathways involved in CAVD that may represent therapeutic targets. Interestingly these pathways are distinct from those associated with vascular smooth muscle and atherosclerosis and further studies in this area may provide for interesting new leads possibly in both pathologies. A pathway identified in CAVD pathology but only associated with vascular development and not yet vascular disease is the canonical Wnt pathway [28, 29]. Low density receptor-related protein (Lrp) binds to the secreted glycoprotein Wnt (a key regulator of bone formation) and frizzled receptors that subsequently activate β-catenin as part of the known signaling pathway in bone mineralization [30]. Wnts are highly secreted, cysteine-rich glycoproteins that are highly conserved among species. They bind to frizzled receptors (Fz) and can be inhibited by frizzled-related proteins (FRP) [29]. VSMCs have been found to express Wnt-5a, Fz-1,2,3 receptors and two inhibitors, FRP-1 and FRP-3 [29]. Although not much is known about the role of Wnt signalling in the vasculature, some studies have demonstrated its role in normal and pathological vessel growth and VSMC proliferation, where Wnt signalling requires the co-receptor, LRP6 [31].

There is substantial evidence that CAVD involves inflammatory processes as has been demonstrated for atherosclerosis, the latter especially in the presence of diabetes [32]. Lesions from early aortic valve sclerosis as well as from advanced calcific stenosis contain macrophages, T-lymphocytes, and mast cells [9, 33]. VCAM-1, which is not normally expressed in aortic valve leaflets, is expressed on the endothelium of calcific aortic valves [34]. Inflammatory cytokines, including IL-1β,
TNF-α, IL-2, HLA-DR and C-reactive protein are also present in valve lesions [8, 35].

The aortic valve tissue response to injury is similar to other tissues with initial elevated TGF-β levels that have been shown in aortic valves myofibroblasts (avMs) in vitro to increase SM α-actin expression, stress fibre formation, contraction, collagen and hyaluronan (HA) synthesis, and secretion of sulfated GAGs [36]. TGF-β can signal through several pathways, classically via high affinity binding to TGF-βRII which recruits the kinase ALK5 (TGF-βRI). ALK5 phosphorylates the carboxy terminal Ser residues of the intracellular signal transducers, SMAD-2 and -3, leading to the formation of phospho-SMADs which form complexes with co-Smads and translocate to the nucleus where they act as transcription factors to activate or repress gene expression. TGF-β is also able to activate the MAP-kinases ERK, JNK and p38. We have recently demonstrated that the action of TGF-β on VSMCs in atherosclerosis involves Smad-2 phosphorylation and activation of p38 MAP kinase [37]. The specific TGF-β pathways in avMs and particularly those participating in CAVD have yet to be elucidated.

The Renin Angiotensin System (RAS) also contributes to the development of aortic valve sclerosis and stenosis [8]. ACE and angiotensin II are co localized with ApoB in valve lesions [11]. The angiotensin-1 receptor, present in normal healthy arteries but not normally expressed in heart valves, is also present in these lesions. There is in vitro evidence that these peptides can be synthesized within the valve [38].

The formation of calcific nodules is a defining pathological occurrence in advanced late-stage valvular sclerotic lesions and results in the leaflets becoming stiff and the valve stenotic which precipitates the clinical condition of CAVD. Calcific nodules are found in association with oxidized lipids both in diseased human valves.
and in animal models of CAVD. Not surprisingly, calcific leaflets contain osteoblast-like cells [33] and an abundance of several osteogenic mediators, including alkaline phosphatase, osteocalcin, osteopontin, BMPs, and MMP2 [39, 40].

Prolonged *in vitro* culture of avMs leads to the spontaneous formation of calcific nodules and again TGF-β plays a prominent role in this stage of disease development [41]. In a specific association with a manifestation of hypertension, avMs exposed to elevated cyclic pressures downregulate the expression of osteopontin; since this agent is protective against mineralization, its down regulation may potentiate calcification [42].
ASSOCIATION OF HYPERTENSION AND CAVD

The association between CAVD and clinical and biochemical factors has been investigated in several studies [1, 43]. Lindroos et al. [43] compared the occurrence of aortic valve disease in elderly subjects as established by echocardiographic and Doppler techniques with the existence of various biochemical and clinical parameters. They investigated 577 subjects ranging from 55-86 years of age. Twenty one subjects (4%) had severe aortic stenosis but 40% and 13% had slight and severe calcification, respectively [43]. Multivariate analysis identified several factors including hypertension which was shown to be an independent and highly statistically significant predictor of CAVD. The odds ratio for hypertension was 1.74 (95% confidence limits of 1.19-2.55) indicating a 74% higher rate of association when hypertension is present. This compares with an 89% increase for a 10 year increase in age and interestingly a 39% increase for each 5 kg.m^-2 decrease in body mass index, the latter associating leanness with predisposition to CAVD. In this study, factors including gender and diabetes were not correlated with aortic valve calcification [43].

In the Cardiovascular Health Study, Otto and colleagues [1] investigated the prevalence of aortic sclerosis and stenosis in the elderly and the clinical factors associated with CAVD. The study covered a randomly chosen group of more than 5000 elderly subjects (≥ 65 years) who underwent 2D echocardiographic investigation and these results were analysed by stepwise logistic regression analysis with a range of clinical parameters [1]. In the entire group, aortic sclerosis and stenosis were present at 26% and 2%, respectively. Disease rates were approximately 50 per cent higher in the group ≥ 75 years of age. A history of hypertension established on a self-reported basis was associated with an excess odds ratio of 1.23 (95% confidence
limits of 1.14-1.32) establishing a highly statistically significant 23% increase in risk. This compares with an increase of 118% for each 10 year increase in age, 103% for male gender and 35% increase for smoking as independent predictors of aortic valve disease. LDL cholesterol, a strong predictor of coronary artery disease had an odds ratio for association with aortic sclerosis and stenosis of 1.12 (95% confidence limits of 1.03-1.23) indicating modest but statistically significant association of this parameter for both coronary artery disease and CAVD [1].

**HYPERTENSION AND ATHEROSCLEROSIS: RELEVANCE TO CAVD**

Hypertension is recognised as one of the strongest independent risk factors for cardiovascular disease [44, 45] and treatments for hypertension are highly efficacious in the prevention of cardiovascular events [15-17]. Hypertension, like other risk factors such as hyperglycaemia, accelerates atherosclerosis leading to increased rates of cardiovascular disease [13, 46]. It is surprising but there is little information on the mechanisms by which hypertension accelerates atherosclerosis. Historically, studies in animal models in the 1980s particularly those that used the spontaneous hypertensive rat (SHR) and its normotensive Wistar Kyoto (WKY) controls, focused on the mechanism of hypertension per se and specific parameters such as the development of vascular hypertrophy [47, 48]. Rats are particularly resistant to the development of atherosclerosis and SHR do not develop atherosclerotic lesions. More recent studies have focused on the genetically modified mice (ApoE<sup>−/−</sup> and LDLR<sup>−/−</sup>) which develop atherosclerosis on high fat diets and the mechanisms of the development of lesions in those mice but the impact of hypertension has not attracted great attention [49]. A major reason for the lack of mechanistic studies on the
association of hypertension and atherosclerosis is due to the fact that hypertension is obviously an in vivo phenomenon which cannot be reproduced in cell culture. There have been studies of blood flow and shear stress and also of cell stretching which partially mimic the parameters associated with hypertension but none is a suitable comprehensive model of hypertension [50, 51].

One of the strongest factors linking hypertension and the accelerated development of atherosclerosis is the activation of the RAS [11]. The RAS is upregulated in hypertension and cardiovascular disease and blocking this system at multiple levels abrogates the development of cardiovascular disease. There is considerable evidence that the actions of the major hormonal effector of the RAS, AII, not only increase blood pressure but also has a range of direct actions which are deleterious to the cardiovascular system. However, based on the multiple roles of AII in causing hypertension, the actions of AII can somewhat narrowly be used as a surrogate for studies of hypertension and the development of atherosclerosis and also potentially for considering the role of hypertension in the development of aortic sclerosis and stenosis.

AII is a potent activator of a wide range of actions on VSMCs which are associated with the development of atherosclerosis [52, 53]. AII stimulates the production and modifies the structure of proteoglycans by vascular smooth muscle cells (VSMCs) [54, 55]. These proteoglycans play a critical early role in atherosclerosis through the trapping of lipoproteins in the vessel wall [24, 56, 57]. AII stimulates the production of reactive oxygen species (ROS) and also many facets of the inflammatory response including the secretion of cytokines and adhesion molecules [58].
There is one major difference between the potential role of AII in atherosclerosis and CAVD. VSMCs in the vessel wall express high levels of angiotensin receptors (associated with vessel tone) and cultured VSMCs express angiotensin receptors to variable levels. In contrast, the avMs of normal aortic valves do not express angiotensin receptors. Unlike VSMCs, early passage avMs do not respond to AII by increasing proteoglycan production (P.J. Little, unpublished observations) [54]. Diseased aortic valves express angiotensin receptors [11]. Thus there would appear to be a clear difference that AII may contribute to early atherosclerosis but as previously proposed its role is likely to be later in the CAVD process [8]. There may be considerably different opportunities for therapeutic intervention in atherosclerosis and CAVD and the underlying pathology will often render earlier intervention preferable in preventing disease initiation and progression. Thus, ACE inhibitors and angiotensin receptor blockers (ARB) may be particularly beneficial in early atherosclerosis (due to effects on blood pressure and direct protective effects on the vasculature). However, the absence of the expression of angiotensin receptors in normal aortic valves might imply that these agents may not have beneficial effects on valves in the early stages of disease development and this is one issue that needs to be resolved clinically [8]. However, it should be appreciated that other potentially beneficial effects of RAS blockade on cardiovascular pathology should not be excluded and the role of blocking the RAS system in preventing CAVD and its consequences should be further investigated and clarified.

Rosenhek et al. reported that ACE inhibitors do not appear to slow the progression of aortic stenosis at a time when statin therapy does have an impact [59]. In view of the expression of angiotensin receptors in avMs in diseased aortic valves this result is quite surprising. Furthermore, the effect of statins may not be related to
plasma cholesterol lowering and may relate to the anti-inflammatory actions of statins. As ACE inhibitors also have anti-inflammatory actions [60], perhaps the anti-inflammatory profiles of ACE inhibitors and statins are sufficiently different to provide some efficacy for statins over ACE inhibitors in CAVD? Clearly further *in vitro* and *in vivo* studies as well as clinical trials are required to determine the impact of drugs on the development and progression of aortic valve sclerosis and stenosis. This includes in clinical setting consideration of the timing of any therapeutic intervention which may not necessarily mean only early therapeutic intervention.

**ANTI-HYERTENSIVE THERAPY AND PREVENTION OF CAVD**

The conjunction of hypertension and CAVD was initially thought to represent a therapeutic conundrum and historically ACE inhibition was considered to be contraindicated in patients with aortic stenosis. It could be reasoned that therapeutic peripheral vasodilatation coupled with compromised cardiac output due to aortic valve stenosis could potentially lead to circulatory collapse. However, although the reasons are unclear, the results of numerous studies indicate that this is a theoretical rather than practical issue [61]. Furthermore, many patients with aortic valve stenosis or at least severe aortic valve sclerosis will already be on blood pressure lowering therapy without apparent compromise. Considerable evidence conclusively indicates that inhibition of the RAS with ACE inhibitors or ARBs has favourable effects on the cardiovascular system, particularly the prevention of left ventricular hypertrophy and cardiac remodelling, both of which are strong risk factors for cardiac disease. Although further information is required before a definite position can be adopted it
would appear that the cardiovascular benefits of RAS inhibition may outweigh the potential for negative outcomes in patients with aortic valve stenosis.

There are no prospective studies available only retrospective observational studies of RAS inhibition and CAVD progression. A recent observational study investigated the relationship between the rate of change of volumetric aortic valve calcium (AVC) scores of patients receiving or not receiving ACE inhibitors [62]. The study investigated 123 patients of whom 43 were on ACE inhibitors and the mean study time was 2.5 years [62]. The patients had undergone two serial electron beam computed tomography (CT) investigations. The rates of change (increase) of AVC scores were statistically significantly higher in the group of patients not receiving ACE inhibitors. The rates of increasing calcium deposition for patients not receiving and those receiving ACE inhibitors were 28.7 %/yr and 11.0 %/yr, respectively. The adjusted odds ratio was a highly significant 29 % in favour of the group on ACE inhibitors. Of interest the prevalence of hypertension was high and the baseline AVC score was statistically significantly higher (146.3 versus 69.5) in the group of patients on ACE inhibitors [62]. It was noted that the association of decreased rates of AVC progression with ACE inhibitors therapy was maintained after adjustment for the higher baseline level of AVC in the ACE inhibitor group. Although a careful interpretation is appropriate this study in total suggests a role for hypertension in precipitating CAVD and a potential role of ACE inhibitors in slowing the progression of disease even in the presence of ongoing hypertension.

Rosenhek et al. have retrospectively evaluated the impact of ACE inhibitors and statins on the progression of aortic stenosis [59]. Of 211 patients, average age 70 years, with confirmed aortic stenosis (peak velocity >2.5 m/s) and otherwise normal cardiac physiology receiving two echocardiograms separated by an average of 24±18
months 102 were on ACE inhibitors, 50 patients on statins and 32 patients on both agents [59]. The increase in annualised peak aortic jet velocity for the entire study group was 0.32±0.44 m.s⁻¹.y⁻¹. ACE inhibitors had no effect on this rate of disease progression either alone or in combination with statin therapy. For comparison, statin therapy markedly and statistically significantly reduced the rate of progression to 0.10±0.41 m.s⁻¹.y⁻¹, and this effect of statins was present in patients with both mild-to-moderate and severe aortic stenosis. In this study 80 percent of the patients had hypertension possibly pointing to a role of hypertension in the development of CAVD notwithstanding the lack of efficacy of ACE inhibitor therapy [59].

CONCLUSIONS

CAVD is now appropriately recognised as a formal disease process and not a result of nonspecific wear and tear based aging of the leaflets. Hypertension is one of the most potent risk factors for atherosclerotic cardiovascular disease and a limited amount of data strongly suggests that hypertension is also associated with the development of CAVD. The development of CAVD has similarities with that of the known processes underlying the development of atherosclerosis but there are appreciable differences in the anatomy, cell biology and indeed based on a limited amount of data, on the response therapeutic interventions. The use of the many classes of anti-hypertensive agents does not give a uniform or consistent response in terms of slowing the development of atherosclerosis and preventing cardiovascular disease. It is preferable at this time that analogies between CAVD and atherosclerosis not be taken too strongly, lest potential treatments for CAVD, related and unrelated to hypertension, be overlooked. However, as always, account must be taken of the range
of actions of drugs on the whole cardiovascular system and not just the disease process in the aortic valve leaflets with the aim of optimising the patient outcome when hypertension and CAVD are present.

ACKNOWLEDGEMENTS

Recent work in the laboratory of PJL has been supported by the National Health and Medical Research Council of Australia, the National Heart Foundation of Australia, and the Diabetes Australia Research Trust.
FIGURES AND FIGURE LEGENDS

Figure 1.

Picture of a complete diseased aortic valve from a patient who underwent aortic valve replacement at The Alfred, Melbourne, Australia in mid 2007. The three leaflets shown are typical and representative of valves from such patients. The view is from the upper or aortic side and the scale shows major divisions in centimetres.
Figure 2A. Stylised structure of a normal aortic valve leaflet

The aortic valve is covered with a layer of endothelial cells which sit on a basement membrane. The elastic lamina lies under the basement membrane. The valve has three layers comprised predominantly of extracellular matrix - the fibrosa layer containing collagen, the spongiosa layer containing glycosaminoglycans (proteoglycans and hyaluronan) and the ventricularis containing elastin. The aortic myofibroblasts are mainly present in the elastin layer, with a random occurrence in the spongiosa. avMs reside mostly across the width of the leaflet but also form perpendicular bundles which make up a cross network in the valve. As drawn, the valve is joined to the heart/aorta at the back of the diagram. The figure here shows a valve leaflet dissected vertically two thirds from the back. The key to the components is shown under Fig. 2B.
In the early stage of CAVD (not shown), the basement membrane is disrupted, endothelial cells are lost and the surface is exposed. The upper elastic lamina gets pushed down as the lesion forms. The lesion contains a large amount of glycosaminoglycans (proteoglycans and hyaluronan). Monocytes in the blood migrate into the valve where they differentiate to form macrophages. Macrophages accumulate lipid leading to foam cell formation. The lesion also contains free lipid droplets. In the end stage of the disease, the thickness of the valve increases. A calcified layer comprising protein and calcium deposits is formed at the base of the lesion. The lesion expands upwards and above the surface of the valve. The top section of the lesion may contain only a few endothelial cells. A photograph of the 3 leaflets of a severely diseased aortic valve is shown in Figure 1.
References


