11

# Ascending Aneurysms in Bicuspid Aortic Valve

Salah A. Mohamed and Hans H. Sievers
*Department of Cardio and Thoracic Vascular Surgery, UK SH-Campus Luebeck, Luebeck, Germany*

## 1. Introduction

The bicuspid aortic valve (BAV), the most common congenital cardiac malformation, is associated with ascending thoracic aneurysms and appears to reflect a common developmental defect. (Hahn et al., 1992; Roberts, 1970) The average time of patients with BAV undergoing surgery (of the aortic valve and/or because of complications associated with it) is a decade earlier than patients with a normally developed aortic valve. Accordingly, it is contended that if a diseased BAV must be replaced because of a diseased BAV, the aneurysmal ascending aorta should also be replaced. Valve replacement surgery without replacing the aorta would simplify the surgical intervention and shorten the time of operation. In contrast, an enlarged ascending aorta represents an increased likelihood of the patient undergoing the same surgical procedure after a few years. Replacing the aortic valve in patients with BAV does not prevent the progressive dilation of the aortic root and ascending aorta. (Yasuda et al., 2003)

Cellular and extracellular processes are involved in the pathogenesis of the ascending aortic aneurysms in patients with BAV. (Bonderman et al., 1999; Mohamed et al., 2010; Nataatmadja et al., 2003; Tang et al., 2005) Many studies have demonstrated the abnormalities of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in aneurysmal tissues. (Boyum et al., 2004; Koullias et al., 2004; Longo et al., 2002) Using tissue microarray techniques, Koullias et al. detected a significantly higher MMP-2 and MMP-9 levels in BAV compared with normal tricuspid aortic valves (TAV), and even significantly higher MMP-2, MMP-9 and TIMP-1 levels compared with all other tissues (control and TAV together). LeMaire et al. observed a lack of inflammatory processes and an increased MMP-2 level and normal MMP-9, TIMP-1 and TIMP-2 expression levels in aneurysmal tissues obtained from patients with BAV. In contrast, in aneurysmal tissues obtained from patients with TAV, they observed increased inflammatory processes and MMP-9 levels. (Lemaire et al., 2005) Furthermore, they showed an increased incidence of cultured vascular smooth muscle cell (VSMC) loss in BAV and Marfan syndrome (MFS) compared with control samples and suggested that a link between the up-regulation of MMP-2 and VSMC apoptosis may exist in MFS. Certainly, there are similarities between the histology of the aneurysmal tissue of the aorta in MFS and that BAV. (Longo et al., 2002) In MFS, a mutation in the gene encoding for the extracellular matrix protein fibrillin-1 can be observed; this mutation leads to dysregulation of the transforming growth factor-beta (TGF-b) signaling. (Dietz et al., 2005) In this chapter, we review the present knowledge for elucidating the ascending aortic aneurysm pathogenesis, particularly in patients with BAV.

We will discuss the genetic basis and basic pathology underlying BAV and ascending aortic aneurysms. We used a simultaneous detection system for MMPs and TIMPs in two different areas of aortic aneurysms to quantify protein levels. Light and transmission electron microscopy were performed in some cases.

## 2. The aorta and its basic structure

The aorta transports oxygenated blood from the heart to the organs of the body. It plays a major role in the biomechanics of the circulatory system. The high velocity pulsatile flow of the ascending aorta changes into a low velocity steady flow when entering the arterioles and capillaries where metabolic processes such as gaseous and nutrient exchange occur. (Lohff, 1999; Olufsen and Nadim, 2004) A healthy aorta has a flexible vasculature and specific size, which correlates with age and gender. Located near the left ventricle, the ascending aorta along with the aortic root forms a unique shape and displays mechanical properties to influence left ventricle workload and coronary blood flow. (Davies et al., 2008; El-Hamamsy and Yacoub, 2009) Similar to all other arterial walls, the ascending aorta comprises three basic layers: the innermost layer, *tunica intima* that adjoins the blood vessel lumen with an endothelial lining; the middle layer, *tunica media* that contains muscular elastic fibers; and the outer layer, *tunica adventitia*. The internal and external elastic laminae (thick elastic fibers) separate these layers from each other. The lamellar unit of the media is the fundamental structural and functional unit of the aortic wall providing viscoelastic properties to the aorta. It is composed of vascular smooth muscle cells between two layers of elastin fibers, which comprise microfibrils and proteoglycans that form the extracellular matrix. (El-Hamamsy and Yacoub, 2009; Wolinsky and Glagov, 1967)

## 3. Present knowledge of genetics of BAV and thoracic aortic aneurysms

Remodeling, processing, and degradation of extracellular matrix proteins are regulated by MMPs and tissue inhibitors of TIMPs. MMPs are a family of zinc-dependent proteolytic enzymes with five major members categorized according to substrates. These members include collagenases, gelatinases, stromelysins, matrilysins, and membrane-type MMPs. (Brauer, 2006; Folgueras et al., 2004) Imbalances in MMP and/or TIMP synthesis have been linked to changes in the aortic wall and formation of aortic aneurysms. (Coady et al., 1999; Davis et al., 1998; Isselbacher, 2005) Although the involvement of MMPs or TIMPs in the pathogenesis of abdominal aortic aneurysms is clarified to a great extent, MMP or TIMP levels in ascending aortic aneurysms have shown different results. (Davis et al., 1998; Goodall et al., 2001; Raffetto and Khalil, 2008) In particular, the elevation of MMPs and TIMPs occurs in ascending aneurysms in BAV. BAV, which was probably first depicted more than 400 years ago in Leonardo da Vinci's sketches, is a genetic disorder. (Clementi et al., 1996; Cripe et al., 2004; Friedman et al., 2008; Huntington et al., 1997; Roberts, 1970) The high heritability of BAV was estimated to be 0.89. Family-based genome-wide analysis revealed linkage of BAV to the chromosomal regions 5q, 13q, and 18q in an autosomal dominant inheritance with reduced penetrance and a non-Mendelian pattern. (Cripe et al., 2004; Huntington et al., 1997; Ward, 2000) Mutations were detected in the transmembrane receptor *NOTCH1* (gene mapped to a locus on chromosome 9q) in familiar and sporadic cases of BAV. (Garg et al., 2005; McKellar et al., 2007; Mohamed et al., 2006) Moreover,

mutations in the *vascular smooth muscle cell alpha actin* gene (mapped to chromosome 10q) have also been identified in patients with BAV and aortic aneurysms. (Milewicz et al., 2008) The *ubiquitin fusion degradation 1-like* gene (mapped to chromosome 22q), which is highly expressed in the outflow tract during embryogenesis, was down-regulated in the cusps of patients with BAV compared with those of control patients. (Mohamed et al., 2005) Furthermore, BAV can manifest as a type of a group of left ventricular outflow tract abnormalities such as aortic coarctation, arch hypoplasia, and supravalvular and mitral valve stenosis. *The homeobox* gene (mapped to a locus on chromosome 5q in humans) *Nkx2-5* deficient heterozygous mice are at a higher risk of developing BAV. (Biben et al., 2000; Wessels et al., 2005) A male predominance of more than 3:1 has been reported for BAV, and this anomaly is very frequent in the X0 Turner's syndrome, with an incidence rate of 22%–34%, suggesting an X-linked etiology. (Miller et al., 1983; Tadros et al., 2009) Analysis of a subpopulation with Anderson syndrome described 4 members (4/41) with BAV. In Anderson syndrome a mutation in the *potassium inwardly-rectifying channel, subfamily J, member 2* (mapped to chromosome 17q) was observed. (Andelfinger et al., 2002) Endothelial nitric oxide synthase (eNOS; located on chromosome 7q in humans) knockout is associated with the development of BAV in mice. (Lee et al., 2000) Kuhlencordt et al. detected a higher incidence of aortic aneurysms in eNOS/apolipoprotein E double-knockout mice. (Kuhlencordt et al., 2001) Aicher et al. reported a significant decrease in the amount of the eNOS protein in BAV aortic tissue compared with that in TAV aortic tissue. (Aicher et al., 2007) The expression and activity of eNOS in aortic endothelial cells is controlled by hemodynamic wall shear stress. Recent studies have indicated that aortic wall shear stress differs locally between BAV and control patients, when examined by magnetic resonance imaging. (Barker et al., 2010; Weigang et al., 2008) Furthermore, we have provided evidence that VSMCs show different apoptotic behavior in the convex and opposite concave portions of the dilated aorta (Fig. 1). Inhibition of caspase-3 protected cultured cells derived from the tunica media of the concavity to a greater extent than those derived from the convexity of the aorta. (Mohamed et al., 2010) These observations that compare of convex and concave ascending aortic sites are extremely important, not only necessarily from a genetic standpoint but also from the standpoint of differential pressures experienced (or more specifically dP/dt) at every site. Early in development, the growth of the embryonic outflow tract (OFT, descendant of the second heart field) shortens at specific stages according to programmed cell death (apoptosis). (Fisher et al., 2000) During cardiac valve formation, when the heart is a simple tube, invaded the extracellular matrix to build the endocardial cushions in the OFT. Migratory cells from pharyngeal arches, i.e., neural crest cells, participate and differentiate into VSMCs that populate the walls of the ascending aorta, aortic arch, head vessels, and interior of semilunar valves. Transient and moderate activities of caspase-3 promote stem cell differentiation; in OFT, only cells with moderate caspase-3 activity undergo smooth muscle differentiation. (bdul-Ghani and Megeney, 2008) It is also our personal belief that dysregulation of apoptosis during valvulogenesis may lead to failure in separating valve leaflets from each other like in BAV. (Zhang et al., 2010).

This present knowledge of ascending aortic aneurysms in patients with BAV reflects only a part of the complex entity of the pathogenesis. BAV occurs at an incidence rate of 1%–2% in the general population, and almost 50% of the anomaly is associated with ascending aneurysms that can lead to aortic dissection or rupture. (Roberts, 1970b; Siu and Silversides, 2010) Therefore, further investigations to understand the pathogenesis of ascending aneurysms are required.

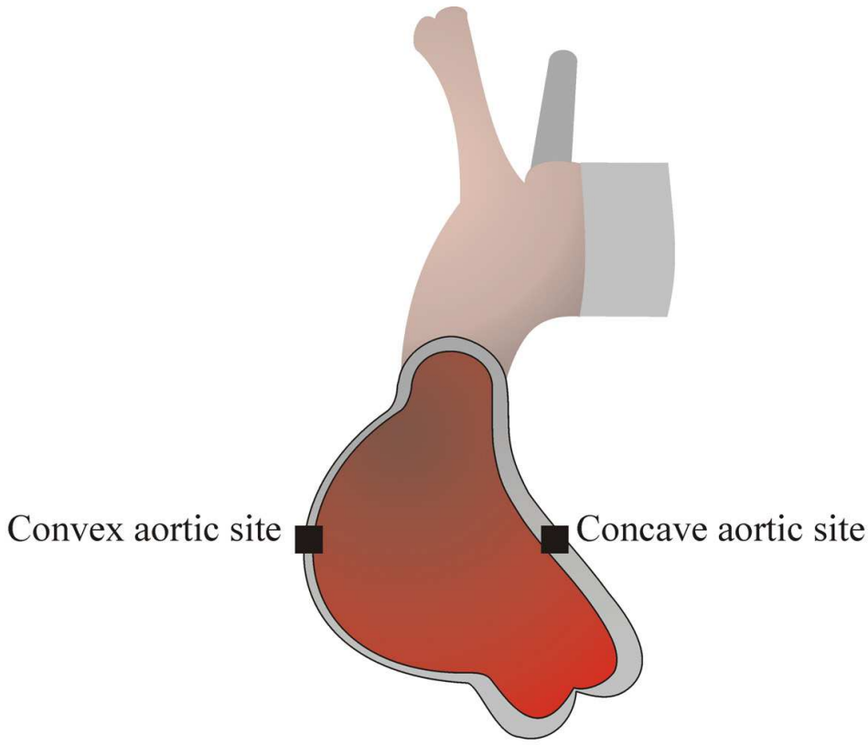



Fig. 1. Schematic representation of ascending aneurysms. Rescted tissue of the concave and convex aortic sites for analysis.

## 4. Simultaneous detection of MMPs and TIMPs in thoracic aortic aneurysms

The mutiplex system (Bio-Plex, BioRad Laboratories, Hercules, CA, USA)) analyses were used to determine the concentrations of MMP-1, MMP -2, MMP -8, MMP -9, MMP -12, and MMP -13 in pg/ml as well as those of TIMP-1, TIMP -2, TIMP -3, and TIMP -4 in two areas of the dilated aorta ascendens (Fig. 1). The Human MMP Fluorokine MultiAnalyte Profiling (FMAP) Base Kit and the respective kits to this panel of targets obtained from R&D Systems (Minneapolis, MN, USA), applied according to the manufacturer's instructions.

Forty-one patients were included in the analysis, the concave and convex aortic sites were identified from overall cases. The group of 31 patients with BAV consisted of 24 male (77%) and 7 female patients, while 7 of the 10 patients with TAV were male (70%). The distribution of age was considerably different between the two groups. Patients with BAV featured a mean age of 50.9 ± 12.9 years and were therefore significantly younger than patients with TAV having a mean age of 63.2 ± 8.2 years ($P$ = 0.006). On the other hand, the means of aortic diameters are comparable (52.7 ± 4.9 mm vs. 56.7 ± 6.6 mm). There were differences in the aortic valve disease between the two groups. While the BAV group contained 10 patients with aortic valve insufficiency (32%), 3 patients with stenosis (10%), and 18 patients with a combination of both diseases (58%), the TAV group comprised patients who only suffered from aortic valve insufficiency.

The overall detection of MMPs and TIMPs using the multiplex system revealed significantly higher MMP-8 and MMP-9 levels in the convex aortic site than in the opposite area (concave) in all patients ($P$ = 0.001; $P$ =.007). On the other hand, MMP-2 and TIMP-3 levels

were elevated in the concave aortic site ($P$ = 0.04, $P$ = 0.0007; Table 1). Patients with TAV have a higher TIMP-3 level in the concave aortic site than in convex aortic site ($P$ = 0.008).

### 4.1 Elevation of MMPs and TIMPs with age

Within the BAV group the age group below and including 51 years displayed a significantly lower expression of TIMP-3 in the convex aortic site in contrast to convex aortic site (10.35 ± 3.4 pg/ml; $P$ = 0.01). The convex area of older patients featured significantly higher MMP-8 and TIMP-2 levels than that of the younger group (10.84 ± 13.92 pg/ml, $P$ = 0.02; 141.91 ± 34.29 pg/ml, $P$ = 0.05).

### 4.2 Elevation of MMPs and TIMPs based on the diameter of aortic aneurysm

To classify patients according to the diameter of aortic aneurysms, the threshold was chosen to be located between 54 and 55 mm, as the mean diameter was 53.7 ± 5.6 mm. Most of the TAV associated aneurysm was larger in diameter than the BAV associated aneurysm. Therefore, all patients with TAV were selected in the group of greater than or equal to 55 mm.

The aortic convex area of patients with BAV suffering from an aneurysm of 54 mm diameter or less, showed a higher MMP-8 and MMP-9 levels compared with the concave area (2.78 ± 2.76 pg/ml, $P$ = 0.04; 9.61 ± 9.78 pg/ml, $P$ = 0.05). The expression of TIMP-3 and TIMP-4 on the other hand is significantly lower in the convex area (11.51 ± 3.81 pg/ml, $P$ = 0.004; 0.25 ± 0.07 pg/ml, $P$ = 0.004). Patients with BAV and an aneurysm with greater than or equal to 55 mm displayed considerably higher MMP-8 and MMP-9 levels in the convex aortic site when compared the concave aortic site (12.30 ± 15.20 pg/ml, $P$ = 0.01, 28.29 ± 41.80 pg/ml, $P$ = 0.04). The TAV group exhibited a higher TIMP-3 expression in the concave when compared with the convex aortic site (10.03 ± 3.50 pg/ml, $P$ = 0.05).

### 4.3 Elevation of MMPs and TIMPs based on gender

Comparison of male and female patients with BAV resulted in a significantly higher TIMP-1 concentration in area 23II of female patients ($P$ = 0.03).

Analyses of the male BAV group resulted in significantly increased MMP-8 and MMP-9 levels in the convex aortic site than in the concave aortic site ($P$ = 0.005; $P$ = 0.01). The concave aortic site showed an elevated TIMP-3 concentration ($P$ = 0.03).

### 4.4 Elevation of MMPs and TIMPs based on aortic valve disease

The classification of patients depending on their aortic valve disease was restricted by the low number of patients with isolated stenosis. Therefore, only patients with BAV with aortic valve insufficiency or a combination of insufficiency and stenosis were considered.

The TAV group comprised patients who only suffered from aortic valve insufficiency.

The BAV group with aortic valve insufficiency showed increased TIMP-3 in the convex aortic site in contrast to concave aortic site ($P$ = 0.02).

The BAV group with a combination of aortic valve disease showed significantly elevated MMP-8 and MMP-9 levels in the convex aortic site ($P$ = 0.004; $P$ = 0.007).

## 5. Light and transmission electron microscopy

In light microscopy, we studied the histopathological features of ascending aortic aneurysms in 15 patients with BAV and 6 with TAV. Convex and concave aortic sites were

graded according to the severity of seven histopathological features: fibrosis, atherosclerosis, medionecrosis, cystic medial necrosis, smooth muscle cell orientation, elastic fiber fragmentation, and inflammation. (de Sa et al., 1999) The most prominent feature is elastic fiber fragmentation (Fig. 2). Aortic ascending abnormalities were more severe in TAV than in BAV. Nonetheless, it became obvious that histological grading of the convex aortic site was generally more severe in BAV, which is associated with the aortic diameter of the convex and not concave aortic sites (Fig. 2). These results correlated with the previous observations of Bechtel et al. (Matthias Bechtel et al., 2003).

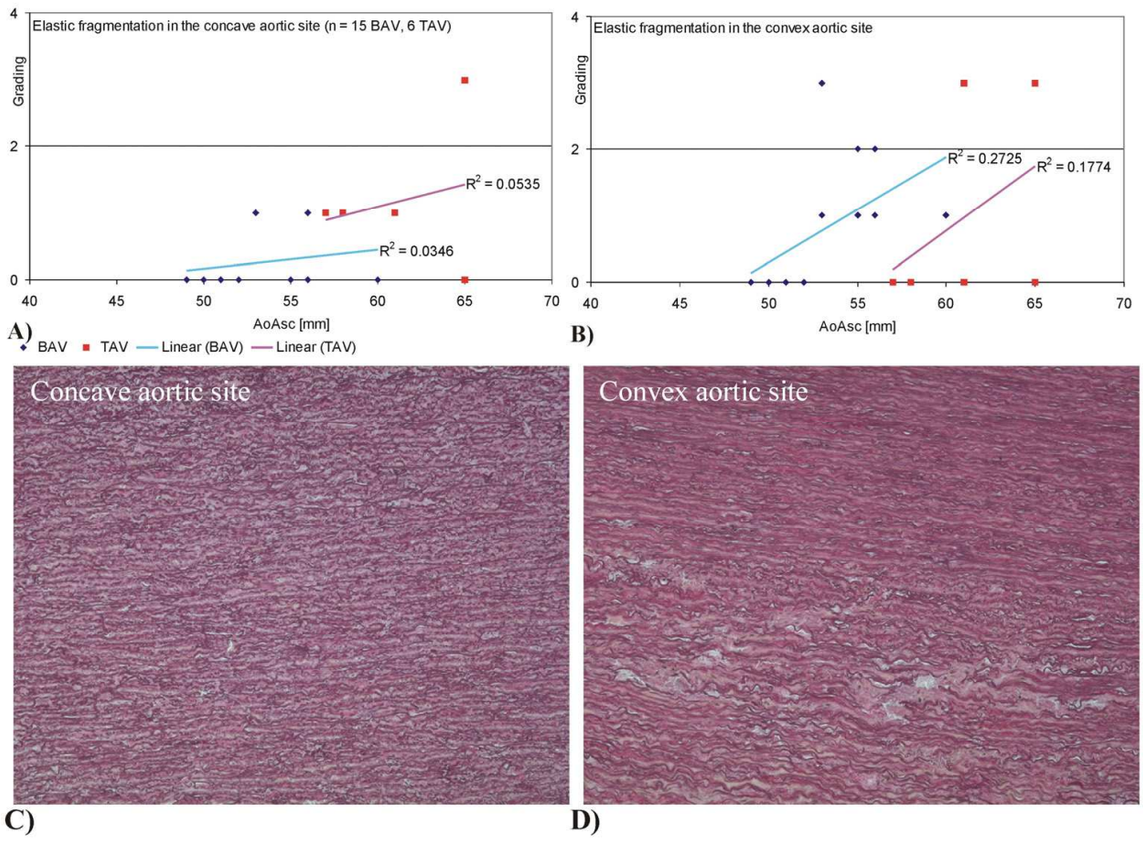



Fig. 2. Elastic fragmentation detected in two sites (concave and convex) of ascending aneurysms of 15 patients with BAV and 6 with TAV. The histopathological evaluation after de SA et al. The histological grading was copared with the aortic diameter (AoAsc; in millimetres) of the concave aortic site in A) and convex aortic site B). Elastica van Gieson staining is demonstrated in paraffin section of aneurysmatic tissue obtained from a 46 year-old-male with BAV thoracic aortic aneurysms (original magnification, x100). In C) the concave aortic site, in D) grade 2 elastic fragmentation of the presence of foci elastic fragmentation in more than five neighboring elastic lamellae of the convex aortic site.

The transmission electron microscopy analysis of the examined slides of aneurysmal tissues obtained from patients with BAV lacks any well known typical structure of the aortic wall. This texture mingles the whole aortic wall as well as the adventitia; the typical build up layer of an aortic wall is not recognisable (Fig. 3A).

In the intima, the endotheliums still possess a single layered consistent coating of plain cells that are aligned parallel to the bloodstream with their longitudinal axis.
The subendothelial layer of the examined specimen exhibits partial extensive differences. This layer contains few cells, at the most long thin stretched processes of fibrocytes, muscle cells are rare. A rather broad layer with a variously running bundle of collagen fibers is attached. The transition to the media is marked through fibrocytes processes, followed by strong bundles of collagen fibers with different orientation. The typical structure of the dense elastic membrane is completely abolished within the media. Bizarre shaped fibrocytes among bundles of collagen fibers, small parts of elastic membranes, and few vascular smooth muscle cells dominate, together with strikingly wide and empty appearing matrix spaces in the TEM. Among all compounds of this series, calcium concrements in all layers of the aortic wall exist as round eosinophilic granules (Fig. 3B).

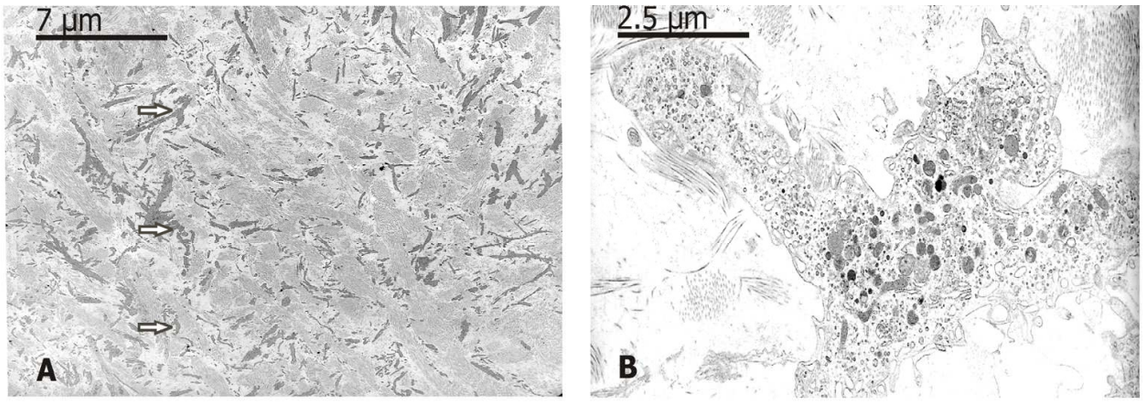



Fig. 3. The transmission electon micropy analysis of the tunica media of the aneurysmal tissue obtained from 15-year-old patient with BAV thoracic aortic aneurysm. In A, the electron micrograph demonstration of the lamellar structure and many broken VSMCs (arrows) with different elongations. In B, a fibaroblast with osmiophilic granules and space vacuoles is demonstrated.

## 6. Discussion

BAV is associated with ascending aneurysms that can lead to acute aortic dissection. (Januzzi et al., 2004) Acute aortic dissection is a life-threatening condition with high morbidity and mortality rates and is generally an unpredictable event. (Abbara et al., 2007; Januzzi et al., 2004; Mohamed et al., 2008; Mohamed et al., 2009; Park et al., 2004; Wheat, Jr., 1987) People commonly at risk of this disease include those with connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, Erdheim–Gsell medial necrosis, and BAV. (Beroukhim et al., 2006; Dietz et al., 1994; Silverman et al., 1995) The exact genetic cause of BAV is unknown. Patients with BAV present a wide spectrum of heterogeneous morphological phenotypes of fused cusps. (Sievers and Schmidtke, 2007)
The normal aorta is a large elastic artery with a wall consisting of the intima and a prominent internal elastic lamina between the intima and media. The media has a markedly layered structure, in which fenestrated layers of elastic lamellae alternate with interlamellar

VSMCs, collagen, and fine elastic fibers. This arrangement is regular so that each elastic lamella and adjacent interlamellar zone is reported as a lamellar unit of the media. In addition to collagen and elastic fibers, the adventitia contains flattened fibroblasts with extremely long processes, macrophages and mast cells, nerve bundles, and lymphatic vessels. On examining the tissue samples of ascending aortic aneurysms of patients with BAV, we observed that the spatial structure of the aortic wall is totally destroyed. This structure was also partly observed during immunohistochemical analysis performed for Marfan syndrome. (Guo et al., 2009) The lamellar units of the media were disintegrated, and the VSMCs were atrophied and wrinkled in a bizarre shape. Between these wrinkled muscle cells, existed thick bundles of collagen fibrils. In some cases of the thoracic aortic aneurysms we detected dramatic changes in the distribution of collagen fibrils in the media with different diameters, and fibroblasts with long and thin processes between the enormous collagen bundles. However, the most striking observation was the lack of elastic fibers. In the adventitia, we observed dysplastic collagen fibrils, which had a flower-like appearance in transverse sections. In addition, accumulations of lipid droplets and eosinophilic granules, probably proteoglycan granules or calcium concrements were observed.

In the literature, different reports exist about matrix protein expression in aneurysmal tissues. In accordance with the published data, we observed the profile of six MMPs and their four inhibitors using a simultaneous detection system in two different areas (concave/convex) of ascending aneurysms. Using this method, we detected and quantified the elevation of MMP-2, MMP-8, MMP-9, and TIMP-1, TIMP-2, TIMP-3, and TIMP-4 in aneurysmal tissues obtained from the concave and opposite convex aortic sites. Concentrations of MMP-1, MMP-12, and MMP-13 were extremely low in these tissues and were therefore omitted. The areas of concave and convex aortic sites were combined in 41 patients (31 BAV and 10 TAV). The patients were divided into group on the basis of age, ascending aneurysm diameter, gender, and valve malformation.

When complete patient data were considered, increased MMP-2 and TIMP-3 levels in the area of the concave (inner curves) aortic site became apparent. The convex area (outer curves) of the ascending aortic aneurysm showed significantly raised MMP-8 and MMP-9 levels. Younger patients (≤51 years) revealed an elevated TIMP-3 level in the inner curves. In addition to the TIMP-3 level, older patients (≥52 years) showed an increase in MMP-2 level in the area of the concave aortic site, and an increase in MMP-8 and MMP-9 levels in the area of the convex aortic site.

Patients with an ascending aneurysm diameter of less than or equal to 54 mm were showed elevated TIMP-3 and TIMP-4 levels in the area of the concave aortic site, whereas aneurysmal convexity showed higher MMP-8 and MMP-9 levels. A aneurysm diameter of greater than or equal to 55 mm was associated with elevated MMP-8 and MMP-9 levels in the ascending aortic wall of the dilated convexity. Comparisons of gender and aortic valve disease groups revealed no significant differences.

In patients with Marfan syndrome, a mutation was observed in the gene encoding ECM protein fibrillin-1 (Dietz and Pyeritz, 1995) and further analysis in this regard may facilitate diagnosis and treatment of this syndrome. The situation differs in patients with BAV because haemodynamics can also play a role, and no defect can be detected in the gene encoding fibrillin-1. Although many studies support the genetic origin of BAV, the genetic pathomechanism of BAV is probably far more complicated possibly due to mutations in different genes.

## 7. Conclusions and future directions

To the best of our knowledge, simultaneous detection of six matrix protein levels was performed for the first time. This method is as accurate as old methods and minimizes the errors that occurred with those methods. Although we did not measure these proteins in blood or body liquids, the results obtained demonstrated that MMPs and matrix proteins can be differently elevated in ascending aortic aneurysms in BAV.

Many factors, such as hemodynamics, environmental factors, and genetic factors (in part) appear to be involved in this process. Other modern technologies such as whole genome screening may identify additional risk factors (single nucleotide polymorphisms); however, these risk factors must also be considered on the basis of their functionality. Another interesting topic for the near future is the microRNAs (miRNAs). miRNAs, small approximately 22 nucleotides in length noncoding nucleotide RNAs, have been shown to modulate mRNA stability and translation. (Cordes and Srivastava, 2009; van and Olson, 2007a; van and Olson, 2007b) In a pervious study, miR-26a was down-regulated in a fused aortic valve. (Nigam et al., 2010) Recently, this miR-26a was also found to be down-regulated in aneurysms. (Leeper et al., 2011)

## 8. Acknowledgements

The author would like to take members of their respective laboratories for helpful discussions. Dr. Kuehnel supported with the transmission electron microscopy analysis. Schoellerman, Schult-Badusche, and Radtke helped with the Bioplex-System. Drs. Wenzel and Pries permitted the use of their platforms. Dr. Noack provided assistance with histological analysis.

## 9. References

Andelfinger G.; Tapper A. R.; Welch R. C.; Vanoye C. G.; George A. L., Jr.; & Benson D. W. (2002) KCNJ2 mutation results in Andersen syndrome with sex-specific cardiac and skeletal muscle phenotypes. *Am J Hum Genet* 71,663-668.

Abbara S.; Kalva S.; Cury R. C.; & Isselbacher E. M. (2007) Thoracic aortic disease: spectrum of multidetector computed tomography imaging findings. *J Cardiovasc Comput Tomogr* 1,40-54.

Aicher D.; Urbich C.; Zeiher A.; Dimmeler S.; & Schafers H. J. (2007) Endothelial nitric oxide synthase in bicuspid aortic valve disease. *Ann Thorac Surg* 83,1290-1294.

Barker A.J.; Lanning C.; & Shandas R. (2010) Quantification of hemodynamic wall shear stress in patients with bicuspid aortic valve using phase-contrast MRI. *Ann Biomed Eng* 38,788-800.

bdul-Ghani M.; Megeney L. A. (2008) Rehabilitation of a contract killer: caspase-3 directs stem cell differentiation. *Cell Stem Cell* 2,515-516.

Beroukhim R.S.; Kruzick T. L.; Taylor A. L.; Gao D.; & Yetman A. T. (2006) Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. *Am J Cardiol* 98,828-830.

Biben C.; Weber R.; Kesteven S.; Stanley E.; McDonald L.; Elliott D. A.; Barnett L.; Koentgen F.; Robb L.; Feneley M.; & Harvey R. P. (2000) Cardiac septal and valvular dysmorphogenesis in mice heterozygous for mutations in the homeobox gene Nkx2-5. *Circ Res* 87,888-895.

Bonderman D.; Gharehbaghi-Schnell E.; Wollenek G.; Maurer G.; Baumgartner H.; & Lang I. M. (1999) Mechanisms underlying aortic dilatation in congenital aortic valve malformation. *Circulation* 99,2138-2143.

Boyum J.; Fellinger E. K.; Schmoker J. D.; Trombley L.; McPartland K.; Ittleman F. P.; & Howard A. B. (2004) Matrix metalloproteinase activity in thoracic aortic aneurysms associated with bicuspid and tricuspid aortic valves. *J Thorac Cardiovasc Surg* 127,686-691.

Brauer P.R. (2006) MMPs--role in cardiovascular development and disease. *Front Biosci* 11,447-478.

Clementi M.; Notari L.; Borghi A.; & Tenconi R. (1996) Familial congenital bicuspid aortic valve: a disorder of uncertain inheritance. *Am J Med Genet* 62,336-338.

Coady M.A.; Rizzo J. A.; Goldstein L. J.; & Elefteriades J. A. (1999) Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. *Cardiol Clin* 17,615-635.

Cordes K.R.; Srivastava D. (2009) MicroRNA regulation of cardiovascular development. *Circ Res* 104,724-732.

Cripe L.; Andelfinger G.; Martin L. J.; Shooner K.; & Benson D. W. (2004) Bicuspid aortic valve is heritable. *J Am Coll Cardiol* 44,138-143.

Davies J.E.; Parker K. H.; Francis D. P.; Hughes A. D.; & Mayet J. (2008) What is the role of the aorta in directing coronary blood flow? *Heart* 94,1545-1547.

Davis V.; Persidskaia R.; Baca-Regen L.; Itoh Y.; Nagase H.; Persidsky Y.; Ghorpade A.; & Baxter B. T. (1998) Matrix metalloproteinase-2 production and its binding to the matrix are increased in abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 18,1625-1633.

de Sa.M.; Moshkovitz Y.; Butany J.; & David T. E. (1999) Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical relevance to the ross procedure. *J Thorac Cardiovasc Surg* 118,588-594.

Dietz H.C.; Loeys B.; Carta L.; & Ramirez F. (2005) Recent progress towards a molecular understanding of Marfan syndrome. *Am J Med Genet C Semin Med Genet* 139C,4-9.

Dietz H.C.; Pyeritz R. E. (1995) Mutations in the human gene for fibrillin-1 (FBN1) in the Marfan syndrome and related disorders. *Hum Mol Genet* 4 Spec No,1799-1809.

Dietz H.C.; Ramirez F.; & Sakai L. Y. (1994) Marfan's syndrome and other microfibrillar diseases. *Adv Hum Genet* 22,153-186.

El-Hamamsy I.; Yacoub M. H. (2009) Cellular and molecular mechanisms of thoracic aortic aneurysms. *Nat Rev Cardiol* 6,771-786.

Fisher S.A.; Langille B. L.; & Srivastava D. (2000) Apoptosis during cardiovascular development. *Circ Res* 87,856-864.

Folgueras A.R.; Pendas A. M.; Sanchez L. M.; & Lopez-Otin C. (2004) Matrix metalloproteinases in cancer: from new functions to improved inhibition strategies. *Int J Dev Biol* 48,411-424.

Friedman T.; Mani A.; & Elefteriades J. A. (2008) Bicuspid aortic valve: clinical approach and scientific review of a common clinical entity. *Expert Rev Cardiovasc Ther* 6,235-248.

Garg V.; Muth A. N.; Ransom J. F.; Schluterman M. K.; Barnes R.; King I. N.; Grossfeld P. D.; & Srivastava D. (2005) Mutations in NOTCH1 cause aortic valve disease. *Nature* 437,270-274.

Goodall S.; Crowther M.; Hemingway D. M.; Bell P. R.; & Thompson M. M. (2001) Ubiquitous elevation of matrix metalloproteinase-2 expression in the vasculature of patients with abdominal aneurysms. *Circulation* 104,304-309.

Guo D.C.; Papke C. L.; Tran-Fadulu V.; Regalado E. S.; Avidan N.; Johnson R. J.; Kim D. H.; Pannu H.; Willing M. C.; Sparks E.; Pyeritz R. E.; Singh M. N.; Dalman R. L.; Grotta J. C.; Marian A. J.; Boerwinkle E. A.; Frazier L. Q.; Lemaire S. A.; Coselli J. S.; Estrera A. L.; Safi H. J.; Veeraraghavan S.; Muzny D. M.; Wheeler D. A.; Willerson J. T.; Yu R. K.; Shete S. S.; Scherer S. E.; Raman C. S.; Buja L. M.; & Milewicz D. M. (2009) Mutations in smooth muscle alpha-actin (ACTA2) cause coronary artery disease, stroke, and Moyamoya disease, along with thoracic aortic disease. *Am J Hum Genet* 84,617-627.

Hahn R.T.; Roman M. J.; Mogtader A. H.; & Devereux R. B. (1992) Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. *J Am Coll Cardiol* 19,283-288.

Huntington K.; Hunter A. G.; & Chan K. L. (1997) A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol* 30,1809-1812.

Isselbacher E.M. (2005) Thoracic and abdominal aortic aneurysms. *Circulation* 111,816-828.

Januzzi J.L.; Isselbacher E. M.; Fattori R.; Cooper J. V.; Smith D. E.; Fang J.; Eagle K. A.; Mehta R. H.; Nienaber C. A.; & Pape L. A. (2004) Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 43,665-669.

Koullias G.J.; Korkolis D. P.; Ravichandran P.; Psyrri A.; Hatzaras I.; & Elefteriades J. A. (2004) Tissue microarray detection of matrix metalloproteinases, in diseased tricuspid and bicuspid aortic valves with or without pathology of the ascending aorta. *Eur J Cardiothorac Surg* 26,1098-1103.

Kuhlencordt P.J.; Gyurko R.; Han F.; Scherrer-Crosbie M.; Aretz T. H.; Hajjar R.; Picard M. H.; & Huang P. L. (2001) Accelerated atherosclerosis, aortic aneurysm formation, and ischemic heart disease in apolipoprotein E/endothelial nitric oxide synthase double-knockout mice. *Circulation* 104,448-454.

Lee T.C.; Zhao Y. D.; Courtman D. W.; & Stewart D. J. (2000) Abnormal aortic valve development in mice lacking endothelial nitric oxide synthase. *Circulation* 101,2345-2348.

Leeper N.J.; Raiesdana A.; Kojima Y.; Chun H. J.; Azuma J.; Maegdefessel L.; Kundu R. K.; Quertermous T.; Tsao P. S.; & Spin J. M. (2011) MicroRNA-26a is a novel regulator of vascular smooth muscle cell function. *J Cell Physiol* 226,1035-1043.

Lemaire S.A.; Wang X.; Wilks J. A.; Carter S. A.; Wen S.; Won T.; Leonardelli D.; Anand G.; Conklin L. D.; Wang X. L.; Thompson R. W.; & Coselli J. S. (2005) Matrix metalloproteinases in ascending aortic aneurysms: bicuspid versus trileaflet aortic valves. *J Surg Res* 123,40-48.

Lohff B. (1999) [1899: the first mathematical description of the pressure-volume diagram by Otto Frank (1865-1944)]. *Sudhoffs Arch* 83,131-151.

Longo G.M.; Xiong W.; Greiner T. C.; Zhao Y.; Fiotti N.; & Baxter B. T. (2002) Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. *J Clin Invest* 110,625-632.

Matthias Bechtel J.F.; Noack F.; Sayk F.; Erasmi A. W.; Bartels C.; & Sievers H. H. (2003) Histopathological grading of ascending aortic aneurysm: comparison of patients with bicuspid versus tricuspid aortic valve. *J Heart Valve Dis* 12,54-59.

McKellar S.H.; Tester D. J.; Yagubyan M.; Majumdar R.; Ackerman M. J.; & Sundt T. M., III (2007) Novel NOTCH1 mutations in patients with bicuspid aortic valve disease and thoracic aortic aneurysms. *J Thorac Cardiovasc Surg* 134,290-296.

Milewicz D.M.; Guo D. C.; Tran-Fadulu V.; Lafont A. L.; Papke C. L.; Inamoto S.; Kwartler C. S.; & Pannu H. (2008) Genetic basis of thoracic aortic aneurysms and dissections: focus on smooth muscle cell contractile dysfunction. *Annu Rev Genomics Hum Genet* 9,283-302.

Miller M.J.; Geffner M. E.; Lippe B. M.; Itami R. M.; Kaplan S. A.; DiSessa T. G.; Isabel-Jones J. B.; & Friedman W. F. (1983) Echocardiography reveals a high incidence of bicuspid aortic valve in Turner syndrome. *J Pediatr* 102,47-50.

Mohamed S.A.; Aherrahrou Z.; Liptau H.; Erasmi A. W.; Hagemann C.; Wrobel S.; Borzym K.; Schunkert H.; Sievers H. H.; & Erdmann J. (2006) Novel missense mutations (p.T596M and p.P1797H) in NOTCH1 in patients with bicuspid aortic valve. *Biochem Biophys Res Commun* 345,1460-1465.

Mohamed S.A.; Hanke T.; Schlueter C.; Bullerdiek J.; & Sievers H. H. (2005) Ubiquitin fusion degradation 1-like gene dysregulation in bicuspid aortic valve. *J Thorac Cardiovasc Surg* 130,1531-1536.

Mohamed S.A.; Misfeld M.; Hanke T.; Charitos E. I.; Bullerdiek J.; Belge G.; Kuehnel W.; & Sievers H. H. (2010) Inhibition of caspase-3 differentially affects vascular smooth muscle cell apoptosis in the concave versus convex aortic sites in ascending aneurysms with a bicuspid aortic valve. *Ann Anat* 192,145-150.

Mohamed S.A.; Misfeld M.; Richardt D.; & Sievers H. H. (2008) Identification of candidate biomarkers of acute aortic dissection. *Recent Pat DNA Gene Seq* 2,61-65.

Mohamed S.A.; Sievers H. H.; Hanke T.; Richardt D.; Schmidtke C.; Charitos E. I.; Belge G.; & Bullerdiek J. (2009) Pathway analysis of differentially expressed genes in patients with acute aortic dissection. *Biomark Insights* 4,81-90.

Nataatmadja M.; West M.; West J.; Summers K.; Walker P.; Nagata M.; & Watanabe T. (2003) Abnormal extracellular matrix protein transport associated with increased apoptosis of vascular smooth muscle cells in marfan syndrome and bicuspid aortic valve thoracic aortic aneurysm. *Circulation* 108 Suppl 1,II329-II334.

Nigam V.; Sievers H. H.; Jensen B. C.; Sier H. A.; Simpson P. C.; Srivastava D.; & Mohamed S. A. (2010) Altered microRNAs in bicuspid aortic valve: a comparison between stenotic and insufficient valves. *J Heart Valve Dis* 19,459-465.

Olufsen M.S.; Nadim A. (2004) On deriving lumped models for blood flow and pressure in the systemic arteries. *Math Biosci Eng* 1,61-80.

Park S.W.; Hutchison S.; Mehta R. H.; Isselbacher E. M.; Cooper J. V.; Fang J.; Evangelista A.; Llovet A.; Nienaber C. A.; Suzuki T.; Pape L. A.; Eagle K. A.; & Oh J. K. (2004) Association of painless acute aortic dissection with increased mortality. *Mayo Clin Proc* 79,1252-1257.

Raffetto J.D.; Khalil R. A. (2008) Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. *Biochem Pharmacol* 75,346-359.

Roberts W.C. (1970) The congenitally bicuspid aortic valve. A study of 85 autopsy cases. *Am J Cardiol* 26,72-83.

Sievers H.H.; Schmidtke C. (2007) A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg* 133,1226-1233.

Silverman D.I.; Burton K. J.; Gray J.; Bosner M. S.; Kouchoukos N. T.; Roman M. J.; Boxer M.; Devereux R. B.; & Tsipouras P. (1995) Life expectancy in the Marfan syndrome. *Am J Cardiol* 75,157-160.

Siu S.C.; Silversides C. K. (2010) Bicuspid aortic valve disease. *J Am Coll Cardiol* 55,2789-2800.

Tadros T.M.; Klein M. D.; & Shapira O. M. (2009) Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. *Circulation* 119,880-890.

Tang P.C.; Yakimov A. O.; Teesdale M. A.; Coady M. A.; Dardik A.; Elefteriades J. A.; & Tellides G. (2005) Transmural inflammation by interferon-gamma-producing T cells correlates with outward vascular remodeling and intimal expansion of ascending thoracic aortic aneurysms. *FASEB J* 19,1528-1530.

van R.E.; Olson E. N. (2007a) microRNAs put their signatures on the heart. *Physiol Genomics* 31,365-366.

van R.E.; Olson E. N. (2007b) MicroRNAs: powerful new regulators of heart disease and provocative therapeutic targets. *J Clin Invest* 117,2369-2376.

Ward C. (2000) Clinical significance of the bicuspid aortic valve. *Heart* 83,81-85.

Weigang E.; Kari F. A.; Beyersdorf F.; Luehr M.; Etz C. D.; Frydrychowicz A.; Harloff A.; & Markl M. (2008) Flow-sensitive four-dimensional magnetic resonance imaging: flow patterns in ascending aortic aneurysms. Eur J Cardiothorac Surg 34,11-16.

Wessels M.W.; Berger R. M.; Frohn-Mulder I. M.; Roos-Hesselink J. W.; Hoogeboom J. J.; Mancini G. S.; Bartelings M. M.; Krijger R.; Wladimiroff J. W.; Niermeijer M. F.; Grossfeld P.; & Willems P. J. (2005) Autosomal dominant inheritance of left ventricular outflow tract obstruction. Am J Med Genet A 134A, 171-179.

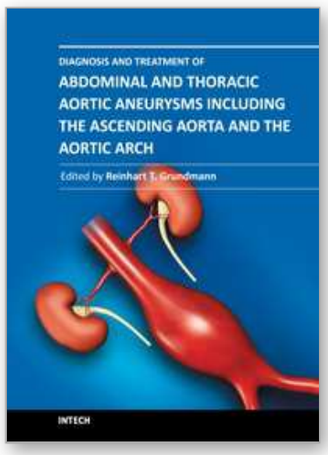
Wheat M.W., Jr. (1987) Acute dissection of the aorta. Cardiovasc Clin 17,241-262.

Wolinsky H.; Glagov S. (1967) A lamellar unit of aortic medial structure and function in mammals. *Circ Res* 20,99-111.

Yasuda H.; Nakatani S.; Stugaard M.; Tsujita-Kuroda Y.; Bando K.; Kobayashi J.; Yamagishi M.; Kitakaze M.; Kitamura S.; & Miyatake K. (2003) Failure to prevent progressive

dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. Circulation 108 Suppl 1,II291-II294.

Zhang J.; Chang J. Y.; Huang Y.; Lin X.; Luo Y.; Schwartz R. J.; Martin J. F.; & Wang F. (2010) The FGF-BMP signaling axis regulates outflow tract valve primordium formation by promoting cushion neural crest cell differentiation. *Circ Res* 107,1209-1219.




**Diagnosis and Treatment of Abdominal and Thoracic Aortic Aneurysms Including the Ascending Aorta and the Aortic Arch**
Edited by Prof. Reinhart Grundmann

ISBN 978-953-307-524-2
Hard cover, 208 pages
**Publisher** InTech
**Published online** 22, June, 2011
**Published in print edition** June, 2011

This book considers diagnosis and treatment of abdominal and thoracic aortic aneurysms. It addresses vascular and cardiothoracic surgeons and interventional radiologists, but also anyone engaged in vascular medicine. The book focuses amongst other things on operations in the ascending aorta and the aortic arch. Surgical procedures in this area have received increasing attention in the last few years and have been subjected to several modifications. Especially the development of interventional radiological endovascular techniques that reduce the invasive nature of surgery as well as complication rates led to rapid advancements. Thoracoabdominal aortic aneurysm (TAAA) repair still remains a challenging operation since it necessitates extended exposure of the aorta and reimplantation of the vital aortic branches. Among possible postoperative complications, spinal cord injury (SCI) seems one of the most formidable morbidities. Strategies for TAAA repair and the best and most reasonable approach to prevent SCI after TAAA repair are presented.



INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen