Dilatation of the ascending aorta in patients with congenitally bicuspid aortic valves

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ABSTRACT

Introduction: The cause of ascending aortic dilatation occurring in patients with congenitally bicuspid aortic valves was investigated.

Methods: Flow patterns through human aortic roots with congenitally bicuspid aortic valves as well as through porcine constricted aortas were studied in a left heart simulator. Vibration was recorded as a measure of turbulence in the post-stenotic segment. Histological changes in fetal aortas with isolated congenitally bicuspid aortic valves were compared to fetal aortas with congenitally bicuspid aortic valves and hypoplastic left hearts, as well as to normal fetal aortas with tricuspid aortic valves.

Results: Congenitally bicuspid aortic valves were anatomically stenotic even in the absence of pressure gradients and without history of relevant symptoms. Histology of the aortic wall in isolated fetal congenitally bicuspid aortic valves was similar to that of fetal aortas with normal tri-leaflet aortic valves, but was abnormal if congenitally bicuspid aortic valves was associated with other cardiovascular anomalies. Flow studies revealed that turbulence and vibration in the post-stenotic aortic segments generated by the stenosis were proportional to the degree of the narrowing.

Conclusions: Congenitally bicuspid aortic valves are inherently stenotic, asymmetrical, generate turbulence and vibration. This not only leads to early failure but also to injury of the ascending aortic wall and ascending aortic dilatation. The more progressive form of ascending aortic dilatation occurs in patients where congenitally bicuspid aortic valves is combined with other inborn anomalies and may require a radical procedure (replacement).

Keywords: bicuspid aortic valve, aortic aneurysm.

INTRODUCTION

Congenitally bicuspid aortic valve (CBAV) is the most common inborn cardiovascular anomaly (1, 2) with a prevalence of 0.9% to 2% in the general population (3). Besides the potential for the early degeneration of the valve itself, CBAV may also lead to ascending aortic dilatation (AAD), dissection and/or rupture (4, 5). The cause of AAD associated with CBAV has been the subject of lively debate in which the participants may be divided into two principal groups: a) those who believe that AAD is caused by flow patterns induced by the abnormal valve (6-10);
b) those who postulate that the AAD is caused by genetic faults which are also responsible for the CBAV itself (11, 12). The principal support to the latter view is that pathological changes and abnormal gene expressions in the aortic wall are often present in patients with CBAV even in the absence of clinical (13) or hemodynamic (14) evidence of stenosis. The purpose of this paper is to present data that reinforces our original stance (6-8) that the changes in the ascending aorta in patients with isolated CBAV are not inborn, but are caused by lifelong bombardment of the ascending aortic wall by turbulence. In patients with CBAV and associated congenital anomalies, this process may indeed be exaggerated by congenital weakness of the ascending aortic wall.

**METHODS**

*Functional morphology.* In vitro experiments were carried out on three cryopreserved then thawed CBAVs obtained from human cadavers with no history of heart disease. Leaflet function was studied in a left-heart simulator (Vivitro Systems, Vancouver, Canada) primed with 38% glycerol, with flow rates set to 2.5-4.0 L/min, aortic pressure at 120/80 mmHg, and a pulse rate of 72 beats/min. The flow rates were measured using electro-magnetic probes (Carolina Medical Electronics). Pressure gradients were determined with appropriate transducers (Transpac IV, Abbott, IL). The function of the valves was visually observed and recorded using axially positioned cameras on both the aortic (500 frames/sec and 30 frames/sec) and ventricular aspects (30 frames/sec). The shape and size of the valve and leaflet movements were studied using intravascular ultrasound (IVUS) for the short axis and an external ultrasound probe for the long-axis views.

*Flow Studies.* Neutrally buoyant seeds were injected into the human CBAVs as well as through six fresh, non-valved porcine thoracic aortas. Using 2D external ultrasound, patterns of the reattachment of the flow-jet to the aortic wall and zones of turbulence were recorded. In the porcine aortas with approximately 20 mm diameters, different degrees of stenoses were created using sections of 3 mm wide Dacron tape. The diameter of the stenoses varied from 7 mm to 2 mm, with induced peak systolic gradients from 20 to 56 mmHg. The porcine aortas were also mounted in the left heart simulator and photographed using a 500 frames/sec cine-camera applying either pulsatile or non-pulsatile flow. Pressure and flow waveforms were monitored (15). The flow patterns through the CBAV were also studied by creating a computer model of bileaflet valves with eccentric orifices, different leaflet lengths and uneven commissure attachments. The model was constructed using Fluent software, as described previously (15).

*Vibration Experiments.* Vibration induced by and used as a measure of turbulence was studied in porcine aortas using a lightweight accelerometer (Model PCB 309A, PCB Piezotronics, Depew, NY) with the sensor glued to the surface of the aorta. The probe was placed 1, 2, 3, 5, and 7 cm distal to the stenosis respectively with the degree of stenosis unchanged. In a second series, the probe was left at each of the locations while the degree of stenosis was varied to create systolic pressure gradients of 20, 38, and 56 mmHg and compared to a background level of vibrations with no stenosis. The sensor output was 5 mV/g, where “g” represents acceleration due to gravity (9.8m/s²). The sampling frequency of the accelerometer was 1000 Hz. The frequency of the vibration was analyzed using fast-Fourier transform analysis (FFT).

*Histology.* Histological analysis of the as-
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In functional morphological studies, Valve A (10 y. o. male) when viewed from the aortic aspect, revealed one leaflet with a prominent raphe, and a prominence near the center of the coaptation line on the other leaflet. The presence of one large and one smaller sinus was obvious. The line of approximation was arched and off-center, resulting in an eccentric orifice. The shape of the fully open orifice was elliptical. Ultrasound imaging also revealed a curved line of closure. When measured via IVUS, the orifice area appeared moderately narrowed (5 – 10%). Valve B (24 y. o. male) had a tiny rudimentary cusp between the two leaflets. In the short axis view, at sinus level, the aorta was elliptical. The line of closure was straight, but the leaflet-coapta-

Figure 1 - Three congenitally bicuspid aortic roots obtained from young individuals who had no symptoms of heart disease and died of non-cardiac causes shown in full diastole (a) and in full systole (b). None of the roots had any measurable trans-valvular pressure gradients. Note the morphological stenosis of various degrees in every specimen. Casts obtained in full diastole (c) shows creases and wrinkles in full diastole.

Figure 2 - Valve C. Ultrasound image showing asymmetrical, elliptical and narrow (57% of the annulus area) leaflet opening.
tion was curved. The open orifice area measured by IVUS was about 75% of that of the annular orifice. Valve C (24 y. o. male), had conjoined leaflets acting as one fused by a prominent raphe and free edge longer than its counterpart (Figures 1 A, B). Both cusps were thin and pliable, with exception of the area toward the raphe. This caused radial shortening. The attachment for the conjoined cusp was flat and scalloped for the other. Measured by IVUS, the orifice was about 55% of the annular area (Figure 2). There was no measurable pressure gradient through any of the valves.

These observations confirmed the wide range of anatomy of the CBAV, especially the asymmetrical geometry of the sinuses. The eccentricity and the stenotic nature of the CBAV are evident even in the absence of clinical symptoms and measurable pressure gradients. Visualization of flow patterns in constricted porcine aortas showed that the flow jet exits the stenosis, creating turbulence and recirculation near the reattach-

Figure 3 - 2D ultrasound images of flow through a vascular stenosis show:

a. The initial jet flow through the stenosis.
b. The development of a recirculation zone.
c. The region of reattachment to the aortic wall.

Figure 4 - Extension of “functional” stenosis past the post-stenotic area (a) and formation of eddy-currents indicated by residual dye in a hydraulic model. Stenosis with post-stenotic dilatation (c) also shows extended “functional stenosis and increase in eddy-currents and turbulence (from Robicsek F, et al: The post-stenotic dilatation of great vessels Acta Med Scand 1954; 155: 481-484).
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ment points to the aortic wall (Figures 3 A, B, C). The tighter the stenosis, the further downstream was the reattachment of flow. Similar turbulence could also be seen in the glass model and was also demonstrated in our earlier experiments (Figure 4).

Compared to normal TAV aortic valves of similar annular dimensions, the orifice of the digital CBAV model was about 50% smaller. By varying the degree of eccentricity, we observed that the more eccentric the model, the more the flow path deviated from the center resulting in increased stress on the longer leaflet.

Under nonpulsatile flow conditions with the CBAV fully opened, the orifice was not only asymmetrical, but also stenotic. This created recirculation of eddy-currents with peak velocity concentrated at the leaflets’ free edge. Unlike a normal TAV, the eddy-currents were not restricted to the sinuses, but extended distally, and were directed toward the right (Figure 5).

Notably, abnormal flow patterns also occur in patients with stenosis of their initially normal TAV. It was reported that in these patients the resulting AAD is symmetrical, “pear” or “teardrop” shaped, while in patients with CBAV, the AAD is convex toward the right antero-lateral aspect, where degenerative media changes were also found to be the most severe (16). These observations agree with our own, in which we found stress-overload at the same location in patients with “normally” function-

**Figure 5** - Symmetrical opening (shaded, clover-shaped area showing maximal leaflet opening) of the trileaflet aortic valves with three even sinuses and leaflets expanding beyond the circumference of the annulus (dotted reversed cone) and the asymmetrical and incomplete (shaded ellipse) opening of the congenitally bicuspid aortic valve with two uneven sinuses. In the latter, the flow-jet impacts the aortic wall.

TAV = trileaflet aortic valves; CBAV = congenitally bicuspid aortic valve.

**Figure 6** - Vibration recordings at 1, 2, 3, and 5 cm from the stenosis. Strongest signal occurs at a frequency of 110 Hz. Vibration is higher at 1 and 2 cm from the stenosis when the pressure gradient is 38 mmHg. Vibration is higher at 3 and 5 cm when the gradient is 56 mmHg.
ing CBAVs with no pressure gradients or regurgitation (15).

Vibrations were the highest 2-3 cm distal to the stenosis, and diminished at a distance of about 5 cm. The dominant frequency was about 110 Hz within a wide range of 20-300 Hz. Higher frequencies were also found, but with less intensity. The amplitude increased proportionally with the pressure gradient.

The higher was the pressure gradient, the further downstream was the maximum amplitude of vibration (Figure 6).

The intensity of vibrations was highest during systolic ejection. Proportional to increased pressure gradient, the point of reattachment of the flow jet, considered to be the force generating vibration, moved distally, indicating that maximum vibration occurs at the site of reattachment of the flow-jet to the aortic wall. With change in pressure and velocity, the point of reattachment moved back and forth, defining the length of aortic segment that was exposed to the most intense vibration (Figures 7-9).

Histological studies of fetal aortas with normal TA V showed normal microscopic anatomy (Figure 8). Histological pictures of the ascending aortas from tri-leaflet and hearts with fetal hearts with CBA V, but no other cardiovascular anomalies, were also within normal range (Figures 10, 11).

**Figure 7** - Different degrees of aortic stenoses, formation of eddy currents, flow reattachment regions and different magnitudes of vibration, leading to development of poststenotic dilatation.

**Figure 8** - Digital re-creation of the flow pattern through bicuspid aortic root and aortic arch.

**Figure 9** - Shear-stress values measured in an aortic arch with a bicuspid aortic valve. Note the high values on the right-lateral aspect of the ascending aorta.
The ascending aortas from the hearts with CBAV and hypoplastic left hearts showed mild intimal thickening, medial hypertrophy and focal elastic tissue disorganization (Figure 12). The distribution of the abnormalities seen in aortic media towards the intimal surface was suggestive that abnormal luminal fluid dynamics contributed to these changes. Microscopic and histological examination of the ascending aorta of a 5 year old boy with CABG, but no other cardiac anomalies showed intimal damage and disintegration of the elastic elements of the ascending aorta (Figure 13).

**DISCUSSION**

The curious phenomenon known as post-stenotic dilatation of arteries was already illustrated in the sixteenth century by the Italian anatomist Giuseppe Morgagni (17) and described in detail by Paget (18); however, it was not studied clinically until 1916 when Halsted described post-stenotic dilatation caused by compression of the subclavian artery by the first rib, and also suggested that it may be caused by “paralysis of the vasomotor nerves and the occlusion of the vasa vasorum” (19). Holman, in
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Since then our theory has been challenged by several authors who identified genetic rather than hemodynamic factors as a cause of AAD in patients with CBAV. One argument forwarded the theory that post-stenotic dilatation is caused by “deceleration of fluid, having passed through a constricted orifice, [which] results in a localized pressure increase” (Bernoulli’s law) (9). Simultaneously, with his presentation we have demonstrated in both in vitro experiments and in clinical observations (6, 7) that blood streaming through stenoses does not decelerate in the immediate post-stenotic segment, but further down; ergo propter, and that there is no localized pressure increase which would explain the dilatation.

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ment to support this view was that AAD and aortic wall changes are often seen in patients with other cardiovascular anomalies (19). Another argument is that patients with CBAV may have anomalies not only in the wall of the ascending aorta, but also in the pulmonary artery. Yet, another argument in favor of the genetic theory is that changes in the ascending aortic wall resembling connective tissue disorders are frequently found in patients with CBAVs and AAD (21, 22).

It also has been suggested that apoptosis (23) and an increase in matrix metalloproteinases may also contribute to the development of AAD (19, 20, 24-27).

We acknowledge the above findings, but not the conclusions drawn. Hereditary tissue disorders, infection, atherosclerosis and most importantly, shear-stress of any origin (23, 28) may cause similar, if not identical, histological and biochemical changes of the aortic wall (29, 30). Thus, the argument that aortic wall changes in adult patients with CBAV resemble those with inborn connective tissue disorders does not prove that these are congenital. In our studies, we were able to differentiate two forms of CBAV: patients with isolated CBAV and those with CBAV combined with other anomalies. In the former group, we found aortic wall changes to be absent at birth, indicating that in these patients AAD develops later and is due solely to turbulent flow.

In the second group, with associated other inborn anomalies, the aortic wall changes are already present in the newborn, and may be exacerbated later by turbulence. The question arises as to how issues of pathogenesis may influence the selection of particular surgical interventions on the ascending aorta in patients with isolated CBAV? Past studies (30) showed that patients with CBAV frequently develop dissection, even if AAD is moderate. Therefore, we agree with the recommendations that the issue of AAD should be surgically addressed if patients, especially those with isolated CBAV, are in need of aortic valve replacement.

Several surgeons, however, who believe that the wall of the ascending aorta is genetically defective in all patients with CBAV, also recommend that patients who are operated upon for symptomatic CBAV should undergo prophylactic ascending aortic replacement, even in absence of ascending aortic dilatation. Others would not replace ascending aortas of normal size, but would graft those that are only moderately (4-4.5 cm in diameter) dilated (11, 32, 33).

CONCLUSION

We demonstrated that ascending aortic wall damages in patients with isolated CBAVs are absent at birth, but develop in later life due to turbulent flow rather than due to inborn connective tissue abnormality. In dilations of a moderate to medium degree, less radical approaches such as aortoplasty, which carries a lower mortality and morbidity rate (34), should be considered (11, 35).

One should also emphasize the key factors of a properly performed aortoplasty, such as a reduction in size to normal (about 3.5 cm in diameter) and, if external reinforcement is used, the wrap should be anchored at the sinus level and extended past the origin of the innominate artery (11, 35). Dilated aortas >6 cm in diameter should be replaced regardless of presence or absence of associated anomalies.

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