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Prevalence and Association of Intracranial Aneurysms in Patients with Bicuspid Aortic Valve Disease

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Bianca Maria Hülser

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Dekan:	Prof. Dr. M. D. Menger
Berichterstatter:	Prof. K. Fassbender
	Prof. J. Schäfers
	Prof. H. Abdul- Khaliq

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Summary / Abstract

Objective: Bicuspid aortic valve (BAV) disease is one of the most common congenital cardiac defects found in the general population and seems to be associated with an increased risk of intracranial aneurysms. Being a connective tissue disorder, it has been suspected to be associated with defects in the connective tissue of arterial walls, since similar diseases such as polycystic kidney disease, Marfan syndrome or Ehlers-Danlos syndrome have already been proven to increase the risk for intracranial aneurysmal occurrence. In order to demonstrate a possible association of the two entities a patient collective with BAV was screened using magnetic resonance imaging (MRI) scanning for aneurysmal detection.

Methods: MRI imaging in order to obtain a threedimensional time-of-flight (3D TOF) Angiography was performed on 60 patients with known BAV (age 30-60 years (mean 51.7 years)). Previous medical history, clinical examination, inclusion and exclusion criteria, risk factors for aneurysmal disease and current medication were documented.

Results: None of the BAV patients screened presented with an intracranial aneurysm (95% confidence interval 0.0%-5.5%), only one was detected extracranially. Compared to the overall prevalence of unruptured intracranial aneurysms in the general population 3.2% (95% confidence interval 1.9%-5.2%) (meta-analysis of 68 studies on 83 study populations, including 94 912 patients from 21 countries) and a study done by Schievink et al. with a similar cohort of 61 patients which revealed with 9.8% (95% confidence interval 2.4%-17.3%) a higher incidence of intracranial aneurysms in patients with BAVs, our patient cohort did not show an increased risk for aneurysmal disease.

Conclusion: In this study no association of intracranial aneurysms in patients with bicuspid aortic valve disease could be demonstrated.

Einleitung: Bikuspide Aortenklappen stellen die häufigste kardiale Fehlbildung in der Bevölkerung dar und scheinen mit einem erhöhten Risiko für das Vorkommen intrakranieller Aneurysmata verbunden zu sein. Diese angeborene kardiale Fehlbildung zählt zu der Gruppe der Bindegewebserkrankungen. Daher wird vermutet, dass zusätzlich zu dem Klappendefekt ein Defekt im Bindegewebe der arteriellen Gefäßwände vorliegen könnte. Insbesondere da bereits gezeigt werden konnte, dass andere Bindegewebserkrankungen, wie die polyzystische Nierenerkrankung, das Marfan-Syndrom oder das Ehler-Danlos-Syndrom, mit einem erhöhten Vorkommen intrakranieller Aneurysmata verbunden sind. Um eine Assoziation beider Pathologien zu untersuchen, erfolgte mithilfe einer kernspintomographischen Bildgebung des Kopfes das Screening von 60 Patienten.

Methoden: Zur Detektion einer möglichen Gefäßmalformation erfolgte die Durchführung einer dreidimensionalen Time-of-flight Sequenz Angiographie an 60 Patienten mit diagnostizierter bikuspider Aortenklappe im Alter zwischen 30 und 60 Jahren (Durchschnittsalter 51,7 Jahren). Vorerkankungen, eine neurologische körperliche Untersuchung, Einschluss und Ausschlusskriterien, Risikofaktoren für die Begünstigung der Entwicklung eines intrakraniellen Aneurysmas sowie die aktuelle Dauermedikation wurden dokumentiert.

Ergebnisse: Bis auf ein extrakraniell lokalisiertes Aneurysma, konnte kein intrakranielles Aneurysma (Konfidenzinterval 95 % (0,0%; 5,5%)) im untersuchten Patientenkollektiv gefunden werden. Verglichen mit der allgemeinen Prävalenz nicht rupturierter Aneurysmata in der Normalbevölkerung, welche bei 3,2% (Konfidenzinterval 95% (1,9%; 5,2%)) liegt (laut einer Metaanalyse, welche 68 Studien, 83 verschiedener Bevölkerungen, 94 912 Patienten aus 21 verschiedenen Ländern umfasst) wurde keine höhere Inzidenz bei Patienten mit bikuspider Aortenklappe in dieser Studie gefunden. Dies steht im Gegensatz zu einer Studie von Schievink et al., die eine ähnliche Patientenkohorte bestehend aus 61 Patienten mit bikuspider Aortenklappe untersuchte und ein höheres Vorkommen (9,8%, Konfidenzinterval 95% (2,4%; 17,3%)) von intrakraniellen Aneurysmata fand.

Schlussfolgerung: In dieser Studie war das Vorkommen intrakranieller Aneurysmata bei Patienten mit bikuspiden Aortenklappen nicht erhöht. Daher konnte in dieser Arbeit keine Assoziation beider Pathologien nachgewiesen werden.

2. Introduction

2.1. Definition, general and gender specific prevalence and aortopathy of bicuspid aortic valves

Bicuspid aortic valves (BAV) are not only one of the most common congenital cardiac malformations[5,19,31,57,58,77] and the leading congenital cause of aortic valve stenosis, but are also associated with an increased risk of aneurysmal disease. Its general prevalence has found to be 1-2 % in the general population[5,19,31,57,58,77] with a predominance for the male gender (male to female ratio 3:1)[20,40,68] with also a higher complication rate in men (i.e. occurrence of aortic regurgitation and aortic dissection).[40]

Bicuspid aortic valves consist of two instead of three, unequally sized cusps, due to an incomplete separation during embryogenesis. Only in recent years, it has become clear, that this valve malformation is far more complex than initially suspected and multiple subtypes have been identified.[49] The most updated classification of BAVs by Sievers and Schmidtke[67] differentiates not only between the morphological but also the functional characteristics of the malformed valve and between valves with or without raphe and the precise location of the fused cusps (e.g. L-R= left and right cusp fusion or R-N= right to non-coronary cusp fusion). The complexity of this classification reflects on the heterogenicity of this pathology.

The genesis of aortopathy associated with BAVs has so far not been definitively identified, however, genetic mutations are thought to play an important role.[49] For example, the chromosome 15q25-26 has been implicated in the genesis of thoracic aortal aneurysms in BAV patients[49] or the NOTCH1 gene[23] has been associated with aortic dilatation in congenital bicuspid aortic valve disease. Yet, the exact number of genes, their specific role and if the same genes responsible for the development of the BAV are also causing BAV associated aortopathy is not fully understood at this point.[49]

2.2. Definitions, types and pathogenesis and pathologic features of intracranial aneurysms

Aneurysms are defined as an abnormal, localized dilatation of a vessel wall. Generally, three types of aneurysms are differentiated: true, false and dissecans.

True aneurysms are a dilatation of all three layers of the vessel wall, with the wall itself still being intact. They vary in size: the diameter of small aneurysms doesn't exceed more than 5 mm, medium to large aneurysms are between 6 and 25 mm and a diameter greater than 25 mm classifies as large. True aneurysms are classified according to their morphology since this is relevant for their treatment. If shaped like a sphere, they are called *saccular* aneu-

rysms, if the dilatation comprises a longer segment of the artery and is diffuse, they are named *fusiform* aneurysms. The saccular aneurysm is the most commonly found intracranial aneurysm and often contains thrombotic material. Due to its typical localization at arterial bifurcations of the circle of Willis (e.g. at the anterior and posterior communicating arteries, the internal carotid artery, the middle cerebral artery and the basilar artery), it is the most frequent cause of subarachnoid haemorrhage (85%).[15]

In false aneurysms a defect in the vessel wall causes blood to accumulate and form a haematoma externally soley bound by extravascular connective tissue.

Cases where blood has separated the layers of the vessel wall and formed a hematoma are classified as a dissection (*aneurysma dissecans*).

There is evidence that two main factors are implicated in the pathogenesis of intracranial aneurysms: *genetics* and *acquired* risk factors.

A *familial aggregation* of intracranial aneurysms was first described in 1954 by Chambers et al.[11] and also more recent studies, analyzing large patient collectives, like Wills et al.[81] (364 Finnish families) were able to provide reliable evidence that a positive family history and therefore genetics must be involved in their development.[81] There have been estimations of an increased risk for first-degree relatives of patients with intracranial aneurysms of as high as 9.8 %. [81] Likewise, an increased risk for subarachnoid haemorrhage in cases of positive family history has been shown.[10] Furthermore a positive family history for brain tumors, pituitary adenoma and atherosclerosis have also been linked.[76] With the fact, that heritable connective tissue diseases have also been associated with aneurysmal disease will be dealt later in this chapter.

Pathophysiologically, defects of one of the vessel layers or the lack of closure of remnant vessel residues during embryogenesis are known causes of congenital aneurysmal disease.

Amongst the *acquired* risk factors arterial hypertension is most commonly connected with the presence of an unruptured intracranial aneurysm, followed by advanced age, cigarette use, female gender, diabetes, coronary artery disease and alcohol consumption.[36]

The acquired risk factors gender and age deserve emphasis at this point. Gender specific differences were demonstrated with a higher prevalence (6%) of unruptured intracranial aneurysms in the female gender with a male to female prevalence ratio of 1.57.[76] Another study evaluating 10,259 autopsies found a female to male ratio of unruptured intracranial aneurysms to be 53:31.[33]

It should be noted here as well, that also the incidence of subarachnoid haemorrhage is with 1.24 times higher in women than in men as well as its secondary complications (risk factor "female gender" for vasospasms: Odds ratio 1.5).[13,15,72,76] These sex related differences apply especially for age groups of advanced age.[72] While in both genders the incidence of aneurysms increases with an age over 30 years[36,76], this incidence is even more pronounced for women, when looking at the advanced age group (age < 50). In males such a significant incline was not found. So in summary, in the age group over 50, the gender differences become even more emphasised.[72,76] A decrease of the overall oestrogen level after menopause und a consecutive decrease of oestrogen receptors has been implicated in this pathophysiology.[29,32,76]

Interestingly, different acquired risk factors can be attributed to certain aneurysmal localizations and therefore varying underlying pathophysiologic mechanisms of intracranial aneurysmal disease have been suspected.[36] Even though Kang et al.[36] showed an overall association of arterial hypertension with aneurysms, in cases of medial cerebral artery aneurysms additionally acquired risk factors, namely age over 50 plus smoking, were present. In females, particularly after menopause, the most common aneurysmal sites were the internal carotid, the posterior communicating artery and the medial cerebral artery bifurcation. The hypothesis here is, that the decreased oestrogen levels have a pathophysiologic influence on the vessel walls. No additional risk factors other than hypertensive disease were found in patients with aneurysms located in the posterior cerebral circuit, whereas smoking and excessive alcohol consumption were more common with aneuryms of the anterior communicating artery.[36]

2.3. The pathobiological hypothesis of rupture and the treatment of intracranial aneurysms

With a prevalence of 3 % in the general population, unruptured intracranial aneurysms of the saccular type are common lesions and are increasingly incidentally detected, due to the wide availability of magnetic resonance imaging.[76] Even though data shows that aneurysms of small sizes (< 5-7 mm) are less likely to rupture[34,69,79], the mortality rate of subarachnoid haemorrhage (its most frequent aetiology being a saccular intracranial aneurysm) is as high as 65 %[79] and permanent posthaemorrhagic disabilities in surviving patients is 50 %.[52]

But what are the mechanisms and the factors favoring a rupture? And how do we determine whether or not to recommend therapy to the patient?

Histopathological examinations of ruptured saccular aneurysms showed a thinned out or nonexistent tunica media and a damaged internal elastic lamina.[4] There is evidence that complex chronic inflammatory processes predispose an aneurysm to rupture. Degenerative processes of the vessel wall with a decrease of wall stabilizing cells (i.e. mural cells) but an excess of myointimal fibrous tissue as well as constant remodeling processes resulting in a disorganized wall structure, have been identified.[21,71] Vessel wall infiltration by immune cells (T- cells, macrophages) triggering a complex cascade leading to vessel wall fibrosis, luminal fibrosis and de-endothelialization are associated with rupture.[21]

Despite extensive research however, the exact pathobiological mechanisms (their exact pathway and sequence) causing aneurysmal rupture, remain unknown.[71]

Yet, there is scientific consensus regarding certain risk factors that should be taken into account when considering treatment options in an aneurysma patient. Several studies show that advanced age (age >60), female gender, Japanese and Finnish ethnicity, aneurysmal size (> 5 mm), aneurysmal location (posterior circulation) and symptomatic (vs. asymptomatic) aneurysm are associated with a higher risk of rupture.[78]

The German Association of Neurology (DGN) aids with scientifically based clear guidelines and recommends interventional treatment only for symptomatic aneurysms with mass effect, independent of aneurysmal size and for asymptomatic aneurysms in the anterior circulation that are at least 7 mm in diameter. For aneurysms in the anterior circulation that are smaller than 7 mm in diameter and are asymptomatic, without previous aneurysmal bleeding, interventional therapy is recommended to be optional. However, in cases of aneurysms located in the posterior circulation, interventional treatment is recommended independent of their size, if the comorbidities, the neurological status of the patient and the risks associated with an intervention, have been weighed against the interventional benefits for the patient. In patients with a positive family history, autosomal dominant polycystic kidney disease or monozygous twins, screening is stated as an option, but not definitively recommended.[70]

2.4. Association of BAV (amongst other heritable connective tissue diseases) with aneurysmal disease (aortic and intracranial)

Over the past few years, several studies were able to demonstrate, that the overall prevalence of aneurysmal disease seems to be much higher in patients with a *connective tissue disorder*.[24,39,76] Vlak et al.[76] compared 68 studies of 21 countries on the prevalence of unruptured intracranial aneurysms and found a higher prevalence of intracranial aneurysms in patients with connective tissue disorders (such as autosomal dominant polycystic kidney dis-

ease). Likewise this was demonstrated for Marfan`s syndrome (prevalence of intracranial aneurysm 14% and its dissection 3%), Ehlers-Danlos syndrome (12%), neurofibromatosis type 1 (11%) and Loeys-Dietz syndrome (28%).[39]

Furthermore scientific data of patients with *bicuspid aortic valves,* classified as a connective tissue disease, shows an association with aneurysmal disease – both the aorta and the intracranial vessels.

Regardless of the haemodynamic turbulences from abnormal valve morphology[9,28,53] a higher incidence of thoracic *aortal* aneurysms in patients with congenital bicuspid aortic valve disease has been established, as well as a higher complication rate from these aneurysms, such as rupture or dissections (8.4 % compared to patients without BAV).[37,50,59] Also in 60% of BAV patients concomitant dilatation of the proximal aorta occurs[28,37,59] and aneurysmal development for the next 25 years, even if not present at the time of BAV diagnosis, was calculated to be 26 %.[50] In summary, coarctation, dilatation and aneurysms of the aorta (all being congenital vascular defects) are common comorbid findings in BAV patients[74] and it should be noted as well, that patients with a coarctation of the aorta (regardless of the presence of a BAV) in turn carry a higher risk for intracranial aneurysms.[22,54,61,65]

Additionally to an increased risk for aortal aneurysms, the same seems to be true for aneurysms affecting the *intracranial* arterial system in patients with BAV. In a study done in the USA with a patient collective of 61 patients with known BAV, the incidence of an intracranial aneurysm was calculated to be 9.8 % higher compared to the general population.[63] A more recent retrospective study including a larger patient collective (n= 678) found a prevalence of 7.7 %, particularly in patients with aortic coarctation present (12.9%).[18]

The evaluation of patients with known intracranial aneurysmal disease for the occurrence of bicuspid aortic valves by Goyal et al.[27] using a large patient collective (n=217) resulted in a prevalence of 0.6%, therefore not underlining the findings of other studies postulating an association of the two pathologies.[18,63] But it showed a connection between intracranial and aortic aneurysmal occurrence (prevalence of 4.7%, regardless of the presence of a BAV).[27] Shaulov et al.[66] were also not able to prove an association of the two pathologies in their patient cohort (n=56) however, they were looking at patients with ruptured aneurysms.

So in conclusion, being classified as a connective tissue disease, bicuspid aortic valve disease is part of a group of pathologies which include the Marfan syndrome, polycystic kidney disease and the Ehlers-Danlos syndrome[6] - all pathologies in which the connective tissue of the whole arterial system can be affected and for which an association with intracranial aneurysms and dissections has already been demonstrated in literature.[22,39,60-62,76]

2.5. Screening methods for intracranial aneurysms

While digital substraction angiography (DSA) is the goldstandard of aneurysmal detection and morphology assessment[14,80] it is not routinely used as a screening method due to its invasiveness and risks. Exposure to ionizing radiation, nephrotoxicity from the contrast agent, persisting neurological deficits due to peri-interventional cerebral thromboembolisms and iatrogenic arterial vessel damage (particularly aneurysm spurium) account amongst the main adverse events.[14,80] Since several studies[12,30,44,51,56] were able to demonstrate a high sensitivity and specificity for intracranial aneurysmal detection for magnetic imaging using the three- dimensional, time-of-flight sequence angiography (3D, TOF MRA) at 3 Tesla, the primary use of the invasive DSA as a screening method is not necessary. The sensitivity of this imaging method was shown to range between 83% and 100%[30,44,51] and its specificity was 97%[56] in several studies using large cohorts. Therefore scientific data shows that 3D TOF MRA is equally accurate and effective in the detection of unruptured intracranial aneurysms compared to DSA[12] as well as a follow- up method in patients who had undergone endovascular aneurysmal treatment.[2] Currently, advances and ongoing research in imaging techniques visualizing the vessel wall structure (additionally to assessing the lumen when using MRA) are made, using the so-called MR-vessel wall imaging (VWI) method.[47] Since, as previously stated, inflammatory pathobiologic mechanisms are hypothesized to play a key role in whether or not rupture of an intracranial aneurysm will occur, this novel imaging technique (by suppressing the signals from blood and cerebrospinal fluid and detecting vessel wall signals) can assess more detailed the vessel wall structure.[45] Scientific data linked circumferential wall enhancement to ruptured saccular aneurysms, whilst no enhancement at all seemed to be a strong indicator for a stable aneurysm. [17,43,46] However, not enough is understood yet about the histopathologic basis of this diverse pathology and the different facets of its presentation on VWI imaging.

2.6. The clinical relevance of an association of BAV with intracranial aneurysms

Since during embryogenesis the heart valves, the structures of the head and neck as well as the arterial system all develop from the same tissue, namely the neural crest[73], one could hypothesize that a genetic defect affecting these tissues may be the underlying cause.[63]

Therefore an association of bicuspid aortic valves not only with aortal aneurysmal disease but also intracranial aneurysms seems plausible, especially since a connective tissue defect is the key pathophysiologic feature in all three pathologies.

Investigating this possible association between BAV and intracranial aneurysms is of great clinical relevance since their early diagnosis and the detection of risk individuals is crucial.

Twelve percent[64] of patients with aneurysmal cerebral bleeding never even reach the hospital and stand a chance for treatment. The mortality rate (as aforementioned) is as high as 65%[79], and due to secondary brain damage half of the patients remain with permanent disabilities.[52] Neuropsychological deficits (e.g. cognitive dysfunction) are common, even in cases where the outcome is considered good.[3,16]

The majority of intracerebral aneurysms are asymptomatic until the time of rupture. Death can occur within minutes and results from the mass effect of a massive subarachnoid haemorrhage or intracerebral bleeding depending on the location of the aneurysm. The high fatality and disability rate of subarachnoidal haemorrhage has already been mentioned before. There are also hypothesis, that the cardiorespiratory centre located within the brainstem is instantly depressed if reached by arterial blood with high pressure.[42] Symptoms of a ruptured intracranial aneurysm may include any kind: resulting from a neurological deficit (cranial nerve deficits, motor and sensory deficits) or severe headache, neck stiffness, photophobia or an altered conscious or mental status.

The diagnosis of an intracranial aneurysm can often only be done postmortem in patients where sudden collapse and death of unknown origin has occurred.[7]

This underlines that only the identification of an asymptomatic intracranial aneurysm ahead of time and the assessment of its risk of rupture, are essential in granting the appropriate treatment. Only then, prophylaxis in the form of either interventional methods (clipping or endovascular coiling) to prevent rupture or monitoring, using MRI control scans at set time intervals can be done.

Therefore the aim of this study was to look into the prevalence of aneurysms in patients with bicuspid aortic valves since this constitutes a connective tissue disorder, as well as to look into a possible association of the two pathologies in a German patient collective to improve the identification of patients at risk.

3. Material and Methods

In this prospective study, 60 patients with known congenital BAV who underwent cardiothoracic surgery were screened using MRI imaging for detection of an intracranial aneurysm. The aim was to establish the prevalence of intracranial aneurysms in patients with a congenital BAV in order to investigate a possible association of the two pathologies.

The study was approved by the local ethics committee (ethics committee of the Saarland University Medical Center, Homburg, Germany, ethics vote no. 98/16) and obeys the laws of the declaration of Helsinki. Every single patient was explained carefully and in detail the aim, content and sequence of this study. Also every patient was informed that it is his or her rightful law to withdraw his or her consent at any point without reason and fear of any negative consequences (please also see the Addendum for detailed information). An informed consent concerning the participation in this study as well as a data protection waiver form was signed by each patient.

First, patients with congenital BAV from the contingent of the department of thoracic and cardiovascular surgery of the Saarland University Medical Center, Homburg, Germany, were identified. Patients between the ages of 30 and 60 years with known congenital BAV, which had undergone valvular surgery at the department of thoracic and cardiovascular surgery of the Saarland University Medical Center, Homburg, Germany, were included. A lower age limit was chosen, since according to current medical data[76], aneurysmal occurrence mainly starts at the age of 30 and in order to reduce comorbidities in our patient cohort, the upper age limit was set to be no older than 60 years.

Patients that were in poor health condition, had a cardiac pacemaker, claustrophobia, pregnant females, patients with the implantation of a cochlear device or cranioplasty containing MRI incompatible and artefact susceptible content, were excluded. None of the BAV patients have had an intracranial aneurysm detected beforehand. However, the majority of patients (45 out of 60) presented with previous aortal aneurysmal disease. 29 patients (25 males, 4 females) presented with both, a preexisting aortal aneurysm plus additional risk factors for aneurysmal development and 16 patients had solely known aortal aneurysms without any other comorbidities. These aneurysms were all located in the proximal part of the aorta ascendens, in a few extending from the aortic root. One patient has had previous dissection of the abdominal aorta.

The patients were counselled concerning the screening for an intracranial aneurysm at the department of neurology, Saarland University Medical Center, Homburg, Germany.

An individual patient sheet was used for each patient where the current and previous medical history, clinical examination, inclusion and exclusion criteria, risk factors for aneurysmal disease, current medication and contact details of the doctor of choice for result transmission were documented.

Aneurysmal risk factors were defined as age, gender, diagnosed arterial hypertension, diabetes mellitus type II, coronary artery disease, current or previous nicotine consumption, alcohol abuse and preexisting aneurysmal disease, known connective tissue disease and preexisting aneurysmal disease.

With every patient the possible finding of an asymptomatic intracranial aneurysm was discussed and careful assessment took place, whether the patient wanted to have knowledge of such a finding or not. This was document for every individual patient.

Then a thorough neurological examination was performed and any neurological deficits found were precisely documented. Informed consent about the MRI investigation as such was sought.

For aneurysmal detection a 3 Tesla MRI Scanner (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) was used to obtain a 3D MR TOF angiography. Additional screening sequences to detect blood degradation productions were added: T1 MPRAGE, T2 axial, T2* axial as well as a DWI sequence.

All MRI imaging studies were reviewed by a neuroradiologist and neurologist as well as independently reviewed a second time by a neuroradiology specialist at the department of neuroradiology at the Saarland University Medical Center, Homburg, Germany.

In cases of incidental imaging findings (e.g. cerebral infarction) where further medical investigation or therapy was needed, further neurological consultation was performed.

The following table (table I) shows a more detailed characterization of the patient collective which was investigated, including their age, gender, previous aneurysmal disease, other predisposing factors for aneurysms and aneurysmal detection.

Table I: Detailed description of age, sex, aneurysmal risk factors and intracranial aneurysm detection of the 60 patients with BAV

Pat. No.	***Age***	***Gender***	***Preexisting aneurysm***	***Other predisposing factors***	***Aneurysm (intracranial) detected***
1	47	m	yes	yes	no
2	30	m	yes	yes	no
3	33	m	yes	no	no
4	59	m	no	yes	no
5	54	m	yes	no	no
6	43	m	no	no	no
7	49	m	yes	yes	no
8	33	m	no	no	no
9	53	m	yes	yes	no
10	54	m	yes	yes	no
11	62	m	yes	yes	no
12	61	m	no	yes	no
13	44	m	no	no	no
14	45	f	no	yes	no
15	50	f	yes	yes	no
16	63	m	yes	yes	no
17	52	f	yes	yes	no
18	41	m	yes	yes	no
19	55	f	yes	yes	no
20	60	m	yes	no	no
21	69	m	yes	yes	no
22	75	m	no	yes	no
23	54	m	yes	yes	no
24	56	m	no	yes	no

25	61	m	yes	yes	no
26	46	m	yes	no	no
27	31	f	yes	yes	no
28	59	m	yes	no	no
29	38	m	no	no	no
30	27	m	no	no	no
31	51	m	no	no	no
32	64	m	yes	yes	no
33	50	m	no	yes	no
34	47	m	yes	no	no
35	39	m	yes	no	no
36	69	m	yes	yes	no
37	46	m	yes	yes	no
38	50	m	yes	yes	no
39	51	m	yes	yes	no
40	57	m	yes	yes	no
41	24	m	no	no	no
42	57	m	no	yes	no
43	48	m	yes	no	no
44	49	m	yes	no	no
45	52	m	yes	no	no
46	69	m	yes	no	no
47	60	m	yes	no	no
48	36	m	yes	yes	no
49	41	m	yes	no	no
50	56	m	yes	no	no
51	61	m	yes	no	no
52	78	m	yes	yes	no
53	71	m	yes	yes	no
54	44	m	yes	yes	no

55	53	m	yes	no	no
56	52	m	no	yes	no
57	60	m	yes	yes	no
58	64	m	yes	yes	no
59	50	m	yes	yes	no
60	73	m	yes	yes	no

4. Results

A total of 60 patients with BAV underwent MRI screening for the detection of an intracranial aneurysm. The mean age of this group was 51.6 years, 55 patients were of male and 5 of female gender. The assessment of aneurysmal risk factors revealed 33 patients with known arterial hypertension, 5 patients with diabetes mellitus type II, 10 patients with nicotine abuse, none with regular and excessive alcohol consumption and 5 patients with previous coronary artery disease.

In 45 patients (41 male, 4 female) preexisting aneurysmal disease, mainly in the form of either an aneurysm of the ascending aorta or aortic arch or previous dissection of the abdominal aorta were found.

29 patients (25 male, 4 female) presented with both, a preexisting aortal aneurysm plus additional risk factors for aneurysmal development. 16 patients had solely known aortal aneurysms and 8 solely risk factors in their previous medical history. So, in total, only 7 out of the 60 patients did not present with preexisting aortal aneurysms. All of them were male. 1 patient had known Marfan syndrome.

For a detailed description of aneurysmal risk factors in this patient cohort please see table II.

Two patients presented with neurological deficits which consisted of hypacusis of the right ear and resting tremor of both hands with the focus being on the left hand, including minimal rigor. These were not related to any intracranial pathology connected with an intracranial aneurysm or any other kind of connective tissue disease or with the previous aortic valve surgery. Furthermore, all together 12 patients presented with previous diseases: 3 patients have had a previous transitory ischemic attack, 5 patients suffered from atrial fibrillation, one patient had an essential tremor and 1 patient bladder cancer without known metastases at the time of screening.

The incidental findings of the MRI screening of these 60 patients are listed in table III. 16 showed cerebral microbleedings, 3 cerebral infarction, which had been clinically silent (one in the right media artery territory, one in both media artery territories and one in the left posterior artery territory), one an arachnoid cyst, one with a lesion of unidentified origin in the brainstem, one with capillary telangiectasia, one with a subependymoma and one with an extracranial aneurysm of the size of 9 mm of the left carotid artery. So in conclusion, the majority of patients (26%) showed cerebral microbleedings and clinically silent cerebral infarction (5%). However, an intracranial aneurysm was not detected in this patient cohort.

Table II: Summary of the results of our patient collective

Data of 60 patients screened	
no. of patients with BAV	60
mean age	51.6 years
M:F ratio	55:5
arterial hypertension	33 *(55.0 %)*
DM II	5 *(8.3 %)*
nicotine abuse	11 *(18.3 %)*
excessive alcohol	none *(0.0 %)*
connective tissue disease	1 (Marfan Syndrome) *(1.7 %)*
neurological deficits	2 *(3.3 %)*
preexisting aortal aneurysmal disease M:F ratio	45 *(75.0 %)* *41:4*
preexisting aneurysm + risk factor M:F ratio	29 *(48.3 %)* 25:4

Table III: Incidental MRI findings in our patient collective

Incidental MRI findings	
cerebral microbleedings	16
cerebral infarction (clinically silent)	3
arachnoid cyst	1
capillary telangiectasia	1
subependymoma	1
extracranial aneurysm	1
lesions of unknown origin	1

5. Discussion

In this patient cohort with a bicuspid aortic valve no intracranial aneurysm was detected (0 out of 60 patients). The general prevalence of unruptured intracranial aneurysm is 3.2 %.[76] This data is derived from the currently largest meta-analysis consisting of 68 studies on 83 study populations, including 94 912 patients from 21 countries for a population characterized by a mean age of 50 years and consisting of 50% male patients.

In medical literature the presence of dilatation of the ascending aorta or the aortic root concomitant to a BAV is suspected to be an indicator for the severity of connective tissue disease.[63] If this is true, the majority of our patient cohort (45 patients) consists of patients with severe BAV disease - still no intracranial aneurysm could be detected. Another subgroup (29 patients, 25 male and 4 female) had preexisting aneurysmal disease plus an additional risk factor for aneurysmal development. So, in this patient collective only 7 out of 60 patients were risk factor free and 53 patients presented with factors, presumably increasing their risk of intracranial aneurysmal development, additionally to their known congenital bicuspid aortic valve. This result does not support the hypothesis, that a congenital bicuspid aortic valve as a connective tissue disease increases the risk of intracranial aneurysm occurrence, at least not in this patient cohort.

Magnetic resonance imaging was the preferred screening method, because of its high accuracy in aneurysmal detection and almost nonexistent associated risks. Compared to computed tomography imaging or digital subtraction angiography there is no radiation exposure. Furthermore, as aforementioned, the chosen imaging technique remains to be accurate and noninvasive. Digital subtraction angiography only remains to be a superior method concerning the visualization of the morphology of a vascular malformation, but did not show to have an advantage concerning accuracy.[12] No contrast media had to be infused, so the risk of an anaphylactic reaction was non-existent. Ethically it was particularly important to avoid high risk exposure of the patients, since undergoing this investigation was merely a dispensable screening process.

The incidental MRI findings of this patient collective match with the common incidental MRI findings in medical literature. Literature describes that the majority of patients (76%) that underwent cardiac surgery, especially if they had preexisting cardiovascular risk factors, show cerebral microbleeds. These are asymptomatic and no neurophysiological decline has ever been linked to this finding.[35,55] The most frequent incidental findings on MRI scans in the general population are asymptotic brain infarcts, followed by benign primary tumors and arachnoid cysts.[75]

Capillary telangiectasia is defined as a cerebral vascular malformation alongside arteriovenous, venous and cavernous vascular malformations.[42,48] It consists of multiple dilated vessels in between healthy cerebral tissues and are often incidental findings on autopsies or MRI imaging.[75] The majority is located in the pons.[42] Even though in the majority of cases they do not seem to be associated with cerebral haemorrhage or any other kind of consequence increasing mortality, there have been rare cases reported in medical literature, where capillary telangiectasia has been identified postmortem as the cause of a major brain bleed.[8,38] Some authors implicate that the neural tissue during embryogenesis plays a role in the development of capillary telangiectasia.[42] It remains unknown, if this finding constitutes just another incidental finding in this patient cohort or if there may be an association of capillary telangiectasia and congenital bicuspid aortic valves.

One patient presented with the finding of an extracranially located aneurysm of the size of 9 mm of the left carotid artery. This raises the question, whether this constitute a further incidental finding or is a clue for a possible association of congenital bicuspid aortic valves and aneurysmal disease. However, to completely clarify this question more systematically investigations on larger patient cohorts are necessary.

However, there are studies with deviant results on this topic. Besides Schievink et al.[63] (2010), a more recent but retrospective study by Egbe et al.[18] published in 2017 supports an association of BAV with intracranial aneurysms. In the study cohort of Schievink et al.[63] 6 out of 61 patients with BAV revealed an intracranial aneurysm upon screening (prevalence of 9.8%). Three of these patients were of female and 3 of male gender. All together 20 women and 41 men were screened with a male to female ration of 38:17 with a mean age being 49.1 years. Egbe et al.[18] reviewed retrospectively 678 patients with BAV - making it the largest study on this topic so far - finding a prevalence of 7.7% (52 out of 678 patients). 198 patients were of female, 480 patients of male gender, the mean age was 57 years. Here a higher risk in patients with coarctation of the aorta, right-left cusp fusion and female gender were identified. Currently, to our knowledge, two more studies exist addressing this issue: one by Shaulov et al.[66] (2012) including 56 patients and one by Goyal et al.[27] (2015) with 217 patients. With a prevalence of 1.8%[66] (1 out of 56 patients) and 0.6%[27] (2 out of 317 patients) respectively, both do not support an association between the two entities. However, it should be noted here, that the patient cohorts screened where different, therefore slightly altering their statement and interpretations compared to this study, Schievink's and Egbe's. Shaulov et al.[66] screened patients with aneurysmal subarachnoidal bleeding for the existence of bicuspid aortic valves, therefore investigating already ruptured intracranial aneurysms. Goyal et al.[27] screened patients with known intracranial aneurysmal disease for the presence of a bicuspid aortic valve.

Factors influencing our findings that might in part explain why our results did not show an association of the two entities, shall be discussed in the following.

A limitation of our study is that the patient cohort with 60 patients is rather small. Even though 53 patients presented with factors, presumably increasing their risk of intracranial aneurysmal development (according to current medical knowledge) additionally to their known congenital bicuspid aortic valve, not a single intracranial aneurysm was detected. A larger cohort may be more ideal for comparison with the general population and therefore be more expressive. However, Schievink et al.[63] were able to demonstrate a rather high prevalence of 9.8% investigating a small patient cohort compared to Egbe`s 7.7% when investigating much more (678) patients[18]. So, whether or not the small number of patients is the essential factor remains unknown, however scientifically the result of a study with a larger patient cohort is more significant of course, always keeping in mind that it was done retrospectively.

The majority of patients (5 out of the 6) with BAV who had an intracranial aneurysm in Schievink's[63] cohort had a concomitant thoracic aortal aneurysm. And even though Goyal et al.[27] were not able to show a significant association between BAV and intracranial aneuryms, but indeed an association of thoracic aortal aneurysms and intracranial aneurysms, this raises the questions whether the high prevalence found by Schievink et al. is due to the fact that there was actually "just" an association of aortal and intracranial aneurysms, rather than with intracranial aneurysms and BAV. If so, this would make a coexistant aortal aneurysm the decisive factor for screening in patients with BAV. Contradicting this point is the fact, that in our study the majority of patients (45 out of 60) presented with a known aneurysm of the aorta and still none of them had an intracranial aneurysm. On a side note it should be mentioned here, that our patient cohort constitutes a considerable patient number with aortal aneurysms that was screened for intracerebral aneurysmal occurrence, which may be a valuable addendum to the existing scientific data. So, in conclusion, deducing from this contradicting scientific data, to what extent thoracic aortal aneurysms are associated with intracranial aneurysms and both in turn with bicuspid aortic valve disease remains unclear.

Secondly, with 5 female and 55 male patients our patient cohort is gender biased. Since the incidence of unruptured intracranial aneurysms seems to be much higher in the female gender with 6.0%[76] (compared to the prevalence of 3% in the general population), this could have influenced our results of not finding an association. The gender bias in our study can simply be explained by the fact that the contingent of the department of thoracic and cardiovascular surgery, Saarland University Medical Center, Homburg, Germany consisted of a majority of male patients since generally the occurrence of congenital bicuspid aortic valves is much more common in the male gender[5,19,31,41,57,58,77]. Yet, Schievink et al.[63] state that they

do not believe that their results were influenced by the risk factor of female sex, since in their cohort still more men than women were screened, which still resulted in a higher incidence of intracranial aneurysms compared to their control group. And even Egbe et al.[18] with 480 patients being male and only 198 patients being female, had a gender bias for the male gender, which, however, given the large patient cohort of 678 patients may not play such a significant role. Having a gender bias in the opposite direction, Goyal et al.[27] (with 80 males and 237 females) still did not find an association of the two pathologies. Therefore the extent of the relevance of the gender bias is not certain. However, a comparison of the 5 female patients of this study with the prevalence in the general population is surely not sufficiently representative, this is another limitation of this study.

Generally, it should also be mentioned that the data[76] generating the prevalence of unruptured intracranial aneurysms in the general population, consists of unruptured intracranial aneurysms which have been detected by different diagnostic modalities. A fact that might alter prevalence data due to varying comparability of the diagnostic tools used. Autopsy studies, MRI imaging (with and without angiography) and intraarterial substraction angiography were included. Whilst retrospective autopsy studies seem to have a lower prevalence (presumably particularly, when it comes to aneurysms of small size), existent data suggests that the imaging modalities of substraction angiography and MRI angiography are relatively well comparable.[12] Also no alterations of prevalence for aneurysmal detection were found, when MRI angiography was used as the initial imaging method.[76] Additionally, minor differences in comparability might not be in grave play when investigating such a large patient cohort of 94 912 patients.

The results of this study (0 out of 60 patients) add in to the current inhomogeneous picture attempting to answer the question, whether or not bicuspid aortic valves are associated with intracranial aneurysmal disease. This becomes particularly evident when scrutinizing the four aforementioned and currently existing scientific investigations of variable sized patient cohorts: Schievink et al. [63] (2010) with 61 patients, Shaulov et al. [66] (2012) with 56 patients, Goyal et al. [27] (2015) with 317 patients and Egbe et al.[18] (2017) with 678 patients. The prevalence rates range between 0.6% and 9.8%. Whilst the study with the largest patient cohort was able to show a significant prevalence, the second largest study showed the lowest prevalence of all four studies, with the remaining two (with similar patient numbers of 56 and 61 patients compared with each other and with this study) showing quite discrepant prevalences with 1.8% and 9.8% respectively, regardless of their cohort number.

Could this be due to BAV, being such a heterogeneous pathology? Epidemiologic, clinical, genetic and molecular data on the genesis of BAV aortopathy itself, still remains very patchy up to this date.[75] This raises the question, if first further research is needed to clarify and

classify the pathogenesis of the aortopathy in BAV patients. Maybe only certain types of BAV aortopathy are associated with intracranial aneurysm predisposition and therefore the type of BAV is the decisive factor for which patients need to be screened or not. Underlining this hypothesis is evidence linking genetics particularly with the pathogenesis of the root phenotype of congenital BAV disease[26] and that different BAV phenotypes differ in their associated risks with the arterial vessel system.[25]

Based on their results, Egbe et al.[18] propose a routine screening for intracranial aneurysms in patients with known bicuspic aortic valves. Since adverse aortic events are associated with BAV[25,26] this along with screening for aneurysms at other locations (e.g. the aorta) seems to be a reasonable suggestion in order to guarantee maximum safety when treating patients with BAV. However, when discussing aneurysmal screening ethical aspects come into essential play. Is it ethically correct to recommend screening for a pathology that is asymptomatic and may remain so until the end of a lifetime? Should we use our advanced technical medical tools for the screening of a disease that might never become relevant for the patient and its knowledge might even unnecessarily worry the patient? Can we even recommend a medical treatment associated with the risk of complications and accept permanent neurological deficits or even death from an intervention that might not even have been necessary?

Especially when it comes for example to predictive genetic testing in Huntington`s disease - a progressive neurodegenerative disease combining motor, cognitive and psychiatric dysfunction- an ethically correct conduct is challenging for the treating physician. It is common consens that the knowledge of having a gene mutation that might generate a disease that is not curable and inevitably will lead to death, is subject to each individuals informed voluntary decision.[1] This reflects the fact, that every human being has the right not to know.

In my opinion, a general recommendation on whether or not patients with BAV should be routinely screened for aneurysmal disease or even for concomitant connective tissue diseases cannot be given with good consciences according to currently available scientific data. A careful evaluation of every individual patient case, taking into account the patients preferences so an informed decision can be made together with the patient, is necessary.

However there is sufficient evidence from a multitude of scientific data from which clear guidelines concerning the screening and treatment methods of unruptured intracranial aneurysms were developed by the German Association of Neurology (DGN).

In conclusion, this study did not confirm the assumption that an existing congenital bicuspid aortic valve increases the risk for the development of an intracranial aneurysm in this patient cohort. Nevertheless, the underlying key for answering this clinically relevant question might lie in further research on the complexity of BAV pathology itself. Only then, more investiga-

tions of larger cohort studies might shed some light on the prevalence and association of intracranial aneurysms in patients with bicuspid aortic valves.

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The results of this study will be submitted for publication with the title *"Prevalence and association of intracranial aneurysms in patients with bicuspid aortic valve disease"* in the Journal of Thoracic and Cardiovascular Surgery.

8. Addendum

Patienteninformation

zur Teilnahme an der Studie zur Inzidenz und Assoziation intrakranieller Aneurysmata mit kongenitalen bikuspiden Aortenklappen

Sehr geehrte Patientin, sehr geehrter Patient,

sie befinden sich in kardiologischer Betreuung, da bei Ihnen von Geburt an eine bikuspide Aortenklappe vorliegt. Normalerweise besteht die Aortenklappe aus drei Segmenten, während sich bei bikuspiden Klappen aufgrund einer fehlenden Separation während der Embryonalzeit nur zwei funktionale Aortenklappen ausbildeten. Das Gewebe, aus welchem die Aortenklappen bestehen ist dasselbe aus welchem die Gefäßwände der weiterführenden Gefäße der Aorta bestehen. Hierzu zählen auch die hirnversorgenden arteriellen Blutgefäße. Häufig zeigen sich verbunden mit der Diagnose einer bikuspiden Aortenklappe Gefäßwandauffälligkeiten an anderen Stellen des Gefäßsystems. Zu diesen Auffälligkeiten zählen auch sog. intrakranielle Aneurysmata. Hierbei handelt es sich um Gefäßwandausweitungen, welche mit einem erhöhten Risiko einer Gehirnblutung einhergehen. Um dieser vorzubeugen kann die vorherige Diagnosestellung eines Aneurysmatas einen erheblichen prognostischen Nutzen haben.

Da nach aktuellem Kenntnisstand eine Häufung intrakranieller Aneurysmata bei Patienten mit kongenitalen bikuspiden Aortenklappen vorliegt, würden wir Ihnen anbieten im Rahmen einer Studie eine kernspintomographische Bildgebung des Gehirns und seiner Gefäße an der Universitätsklinik zu organisieren.

Bei dieser Untersuchung handelt es sich um bildgebende Modalität, bei der mit Hilfe eines Magnetfeldes Radiowellen erzeugt werden, welche auf bestimmte Körperbereiche geschickt werden (in Ihrem Fall der Kopf) und die entstehenden Echosignale gemessen werden. Ein Computer erstellt daraus Querschnittbilder. Eine ergänzende Magnet- Resonanz- Angiographie ermöglicht es die Blutgefäße darzustellen. Für die Untersuchung werden Sie auf einer Liege in einer ca. 60 bis 80 cm großen Öffnung liegen. Laute Klopfgeräusche während der Untersuchung entstehen durch die elektromagnetische Schaltung und sind völlig normal, sie werden jedoch Ohrstöpsel sowie Kopfhörer erhalten. Die durchschnittliche Untersuchungszeit liegt zwischen 20 bis 40 Minuten. Obwohl es sich bei einer Kernspintomographie um eine harmlose, nichtinvasise Untersuchung handelt, können beispielsweise Schwellungen oder ein Wärmegefühl durch metallhaltige Farbstoffe von permanent Make-up oder Tätowierungen, Ohrgeräusche, welche zumeist nach der Untersuchung wieder verschwinden, können auftreten.

Es werden keine zusätzlichen, über die o.g. MRT Bildgebung hinausgehenden Untersuchungen durchgeführt.

Im Falle des Vorliegens einer Gefäßauffälligkeit wird ein ausführliches, interdisziplinäres Beratungsgespräch bzgl. des weiteren Vorgehens erfolgen.

Zudem bitten wir Sie um Ihre Einwilligung, dass Ihre personenbezogenen Daten in pseudonymisierter (verschlüsselter) Form für wissenschaftliche Zwecke verwendet werden dürfen (siehe beiliegende Datenschutzerklärung).

Ein Aussteigen aus dieser Studie ist für Sie ohne Angaben von Gründen jederzeit möglich.

Datenschutzerklärung

Inzidenz und Assoziation intrakranieller Aneurysmata mit kongenitalen bikuspiden Aortenklappen

Mir, ……, ist bekannt, dass bei dieser klinischen Verlaufsbeobachtung personenbezogene Daten, insbesondere medizinische Befunde, über mich erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über meine Gesundheit erfolgt nach den gesetzlichen Bestimmungen und setzt vor der Teilnahme an der Studie folgende freiwillig abgegebene Einwilligungserklärung voraus:

Einwilligung zum Datenschutz

Ich willige ein, dass im Rahmen dieser klinischen Studie erhobene Daten, insbesondere Angaben über meine Gesundheit in Papierform und auf elektronischen Datenträgern in der Universitätsklinik des Saarlandes, Klinik für Neurologie sowie Klinik für Neuroradiologie aufgezeichnet werden. Ich willige ein, dass diese Daten in pseudonomysierter (verschlüsselter) Form für wissenschaftliche Zwecke und für die Veröffentlichung auf Kongressen oder in wissenschaftlichen Fachzeitschriften verwendet werden können.

Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten, insbesondere der Daten über meine Gesundheit, ist widerruflich. Ich bin bereits darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an der klinischen Prüfung beenden kann. Im Fall eines solchen Widerrufs meiner Erklärung an der Studie teilzunehmen habe ich das Recht die Löschung meiner bis dahin erhobenen Daten ohne vorherige Prüfung zu verlangen.

Ich willige ein, dass meine Daten nach Beendigung oder Abbruch der Prüfung mindestens 10 Jahre aufbewahrt werden, wie es die gesetzlichen Vorschriften vorsehen. Danach werden meine personenbezogenen Daten gelöscht.

Falls ich meine Einwilligung, an dieser Studie teilzunehmen widerrufe, müssen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten, gespeichert haben, diese unverzüglich löschen.

Homburg, den …….

……..

Name des Patienten und Unterschrift

Studie: ***Assoziation und Inzidenz bikuspider Aortenklappen mit intrazerebralen Aneurysmata***

Patient: …… Datum:

Geb.: …… Ärztin: B. Schmidl

Pat.Nr.: .....

Diagnosen: ……..

Relevante Vordiagnosen: ……..

……..

……..

Kontraindikationen/ Ausschlusskriterien:

- Herzschrittmacher
- Cochleaimplantat
- Klaustrophobie
- Schwangerschaft

Risikofaktoren:

- Alter:
- Weibliches Geschlecht
- Arterieller Hypertonus/ RR Medikation
- Diabetes mellitus Typ II
- Koronare Herzkrankheit
- Ex- oder aktueller Nikotinabusus
- Übermäßiger Alkoholkonsum
- Aneurysmata bereits vorbestehend (z.B. Aorta ascendens, Aortenwurzel)

Vormedikation:

Neurologischer Untersuchungsbefund:

cMRT Befund:

- **vorläufiger Befund bereits mitgeteilt, endgültigen Befund nachschicken**
- **noch kein Befund mitgeteilt**

Intrakranielles Aneurysma im endgültigen cMRT Befund:

- **ja, Beratungstermin am:**
- nein

Aus datenschutzrechtlichen Gründen wurde der Lebenslauf für die Veröffentlichung entfernt.