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Editorial

Can transforming growth factor beta and downstream signalers distinguish bicuspid aortic valve patients susceptible for future aortic complications?

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ABSTRACT

Patients with a bicuspid aortic valve have an extreme high risk to develop a thoracic aortic aneurysm and dissection (TAAD). TAADs form a leading cause of death worldwide, with the majority of deaths being preventable if individuals at risk are identified and properly managed. Risk stratification for TAADs in bicuspidy is so far solely based on the aortic diameter. Exclusive use of aortic wall dimension, as in the current guidelines, is however not sufficient in selecting patients vulnerable for future aortic wall complications. Moreover, there are no effective medical treatments for TAADs to retain progressive aortic dilatation and thus prevent or delay aortic complications. Only surgical replacement of the aorta increases life expectancy in patients with a risk for a TAAD. Therefore, the next major challenge in the management of TAADs is the development of a personalized patient-tailored risk stratification for early detection of patients with an increased risk for TAADs, who will benefit from surgical resection of the aorta. Several signaling pathways have been studied in recent times to develop a patient specific risk stratification model. In this paper we discuss TGF-β signaling and downstream signalers as potential markers for future aortic complications in bicuspid aortic valve patients.

Patients with a bicuspid aortic valve (BAV) have an increased risk to develop a thoracic aortic aneurysm or dissection as compared to patients with a normal tricuspid aortic valve (TAV) [1,2]. Histopathological similarities between thoracic aortopathy in genetic syndromes (i.e., Marfan syndrome, Loeys-Dietz syndrome) and bicuspid aortopathy have recently been described such as dedifferentiated vascular smooth muscle cells (VSMCs) and a significantly thinner intimal layer [3,4]. Marfan and Loeys Dietz syndrome are characterized by defects in the Transforming Growth Factor (TGFβ) ligands, receptors (TGFβR1/2) and their pathways (e.g., SMAD2/3). A number of recent publications have addressed the pathobiology of BAV-related aortopathy however, the role of TGF-β signaling in identifying patients at risk for aortic complications has not yet been fully elucidated.

In earlier publications an altered serum TGF-β expression had been described in BAV patients [5–7] (Table 1). These findings were however difficult to interpret as TGF-β has a wide variety of remodelling functions and an increased bioavailability in the serum cannot be seen as specific for aortic pathology. Moreover, identifying the precise role of altered TGF-β and downstream signaling in aortopathy is challenging because of a wide array of age- and time-dependent phenotypes and the compensatory function of multiple TGF-β isoforms. Nevertheless, several recent studies are commendable in their effort to investigate differences in the TGF-ß signaling pathway of the ascending aorta between degenerative and congenital aortopathy in TAV and BAV patients respectively. In this paper we give an overview of the current literature and highlight knowledge gaps which should be addressed in future.

Studies focusing on the TGF-β signaling pathway in BAV patients on tissue level found a decreased expression of TGF-β and the downstream signalers phosphorylated SMAD2 (pSMAD2) and SMAD3 (pSMAD3) in the non- and dilated aorta of BAV patients [8–10] (Table 1). Recently, Balint et al also found that in the dilated aorta of BAV patients the expression of TGFß1 is significantly lower as compared to the dilated TAV patients [11]. Interestingly, the authors described that in BAV patients the pSMAD2/pSMAD3 and TGFß1 expressions were not correlated [11] (Table 1). In our

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Table 1
Studies suggesting TGF-ß as a potential biomarker for BAV associated aortopathy

Study population	Method to study TGF-ß1 expression	Levels in BAV	Aortic valve pathology	Ref.
Non- and dilated BAV and TAV patients	Serum levels of TGF-ß1	- Increased TGF-ß1 expression in dilated vs non-dilated BAV specimen (ns) - No difference between BAV and TAV	Results not corrected for valve pathology	[4]
Non- and dilated BAV and TAV patients	- Serum levels of TGF-β1 and endoglin - Gene expression of TGF-β1, MMPs and endoglin in aortic tissue samples	- Decreased TGF-β1 expression in non-dilated BAV vs healthy controls - Increased endoglin/ TGF-β1 ratio in BAV vs healthy controls	Aortic stenosis	[5]
BAV patients (aortic diameter not specified)	Serum levels of TGF-ß1	- Increased Serum levels of TGF-ß1 in BAV versus patients without genetic aortic syndromes	Unknown	[6]
Non-dilated BAV and TAV patients	Aortic tissue expression of TGF-ß1, TGFβR1 and 2	- Increased TGFβ, and TGFβR2 expression in dilated BAV vs healthy controls - Decreased TGFβR1 in dilated BAV vs healthy controls	Aortic stenosis	[7]
Non- and dilated BAV and TAV patients	- Aortic tissue expression of TGF-ß1, pSMAD2 and pSMAD3 - Specific analysis within the non-dilated BAV patient group	- Non-homogeneous expression of TGF-ß: mainly in the outer media, absent in the inner and middle media - TGF-ß as susceptibility marker for future aortopathy - pSMAD2 expression in the complete media, not correlated to TGF-ß expression - Lack of TGF-ß and pSMAD2 expression in the intima	Unknown	[8]
Dilated BAV and TAV patients	- Gene expression of TGFβ in aortic smooth muscle cells - Aortic tissue expression of TGFβ and SMAD	- Different TGFβ gene expression BAV vs TAV - Lower TGFβ and SMAD expression in BAV vs TAV	Unknown	[9]
Non- and dilated BAV, TAV and UAV patients	- Aortic tissue expression of TGF-ß1, pSMAD2 and pSMAD3	- Increased TGFß1 expression in non-dilated BAV vs TAV - Decreased TGFß1 expression in dilated BAV vs TAV - No correlation with pSMAD2/3	Unknown	[10]

Abbreviations: BAV: bicuspid aortic valve, MMPs: matrix metalloproteinases, ns: non-significant, pSMAD: phosphorylated SMAD, TAV: tricuspid aortic valve, TGF-ß1: transforming growth factor beta, TGFβR: transforming growth factor beta receptor, Ref: reference, UAV: unicuspid aortic valve.

previous study, we reported a non-homogenous expression pattern of TGF-ß in the aortic wall. We found that TGF-ß is mainly expressed in the outer media and that the inner and middle media are completely devoid of TGFß. Phosphorylated SMAD2 on the other hand was found in the complete media, including the inner and middle media, confirming that the medial phosphorylated SMAD2 expression is independent of TGF-ß [9,11]. We also found that the expression of TGF-ß and pSMAD2 was significantly lower in the outer media of the ascending aortic wall in the dilated BAV and a subset of non-dilated BAV patients, suggesting a marker of future susceptibility for aortic dilatation [9]. Furthermore, in our BAV aortic wall specimen the intimal layer was completely devoid TGF-β expression and the downstream signaling factor pSMAD2, in contrast to the significantly higher expression in the TAV intima.

The abovementioned specific expression patterns of TGF-β and downstream signalers in the ascending aortic wall, can be associated with characteristic pathological features in the BAV and warrants further attention. Firstly, BAV patients have an embryonically determined phenotypic switch defect of the vascular smooth muscle cells [1,3,12]. It has been shown in both human and mice that a lack of TGFβ1 activation decreases VSMC contractility [13], which is in line with the decreased TGF-β activity observed in the BAV aorta. Secondly, the BAV is characterized by a lack of intimal thickening, where it is also known that TGF-β plays a crucial role in the development of the intimal layer. Considering the prominent role of TGF-β in the development of vascular smooth muscle cells and intimal layer, it is thus plausible that in the BAV patients a defect in the TGF-β signaling pathway is responsible for the lack of phenotypic switch of vascular smooth muscle cells and intimal thickening after birth.

The intimal and medial defects are however typically seen in all BAV patients and are therefore not specific to those with an increased risk for thoracic aortopathy.

Due to the high risk for lethal aortic complications in a large subset of BAV patients, identification of patients which could benefit from a preventive aortic replacement is considered an urgent medical need. Currently, the only way to detect patients at risk is by a geometrical criterium. Recent studies have however shown that an acute aortic dissection can occur even in the absence of aortic dilatation. For an optimal monitoring of disease progression and proper timing of aortic surgery we need prognostic biomarkers which could provide additional information to determine who is at highest risk for future complications. In this paper we provide an overview of studies which suggested the TGF-ß signaling pathway as a potential biomarker to detect patients susceptible for aortopathy. Even though a defective TGF-ß signaling was reported in BAV patients, most studies focused on the histological and biochemical differences between dilated aortic walls of BAV and TAV patients (Table 1). Aneurysmal tissue should however be considered as end-stage disease, making it impossible to distinguish whether the observed features are the cause or effect of aortic dilatation. Moreover, in most studies which investigated differences in TGF-ß expression between the BAV and TAV, the underlying aortic valve pathology was not considered (Table 1). As stenotic BAV aortopathy is characterized by mild pathological aortic features as compared to aortic regurgitation [14], the underlying aortic valve pathology should also be taken into account while analyzing differences in expression patterns.

Considering the prominent role of TGF-ß in vascular remodeling and important pathological features in BAV, we suggest future studies to focus on the abovementioned factors to take a step towards personalized risk stratification. To identify potential biomarkers for future aortopathy in BAV, we recommend to study TGF-ß and downstream signalers in non-dilated aortic specimen to distinguish differences in expression pattern. Data should be correlated with the valve pathology (i.e., stenosis and/ or regurgitation). Longitudinal follow-up is needed to investigate the prognostic value of the biomarkers to identify patients with an increased risk for future aortopathy who will benefit from a preventive surgical treatment.

Declaration of Competing Interest

None.

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