

Risk factors for paravalvular leak after transcatheter aortic valve implantation



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Abstract

Many studies have shown that transcatheter aortic valve implantation (TAVI) improves outcomes in patients with severe aortic stenosis in whom a classical surgical procedure cannot be performed due to the high risk. As one of the most frequent periprocedural complications of TAVI, paravalvular leak significantly affects the short- and long-term prognosis for patients undergoing implantation. In this paper, we analyze the most significant anatomical and procedural predictors of paravalvular leak after TAVI.

Key words: TAVI, risk factors, paravalvular leak.

Streszczenie

Badania wykazały, że przezcewnikowa implantacja zastawki aortalnej (*transcatheter aortic valve implantation – TAVI*) wydłuża przeżycie w grupie chorych z ciężką stenozą aortalną, u których zabieg chirurgiczny obarczony jest zbyt dużym ryzykiem operacyjnym i nie może być wykonany. Jednym z najczęstszych powikłań po TAVI jest przeciek okołozastawkowy, który istotnie wpływa na rokowanie krótko- i długoterminowe u pacjentów poddanych temu zabiegowi. W pracy przeanalizowano najważniejsze czynniki anatomiczne i proceduralne, które wpływają na występowanie tego powikłania po TAVI.

Słowa kluczowe: TAVI, czynniki ryzyka, przeciek okołozastawkowy.

Introduction

The method of transcatheter aortic valve implantation (TAVI) introduced in 2002 by Alain Cribier *et al.* has offered new prospects for patients with severe aortic stenosis and multiple comorbidities, for whom surgical procedures are associated with exceedingly high operative risk [1, 2]. The randomized multicenter PARTNER trial (Placement of AoRtic TraNscathetER Valve Trial) proved that TAVI is an alternative for surgical aortic valve replacement (SAVR) for high-risk patients; it is characterized by similar mortality and results in terms of reducing the symptoms of stenosis, but it is associated with a higher incidence of paravalvular leak (PVL) [3].

The presence of aortic regurgitation (AR) jet from the aorta into the left ventricle is the most common complication after TAVI, occurring in as many as 70% of patients; notwithstanding, its grade is usually trivial or mild [4, 5]. In most previous studies, mild AR was not associated with significantly shorter survival time [4, 5]; however, the PARTNER trial demonstrated that it may be associated with worse

long-term prognosis [3]. Significant AR (moderate and severe) is less common, occurring in approximately 15-20% of cases [6], and is one of the most important prognostic factors of mortality during short- and long-term follow-up [7, 8]. It is, therefore, essential to understand the mechanisms and risk factors associated with the occurrence of AR in order to minimize its incidence.

Most cases of AR after TAVI are associated with PVL. Transvalvular regurgitation (TVR) occurs much less frequently and is sometimes concomitant with PVL [8-10]. Some authors do not distinguish between these two types of regurgitation. Nonetheless, the mechanisms specific for the development of TVR will not be the subject of this paper since significant TVR is a much less frequent complication whose pathophysiological mechanism is different from that of PVL.

Paravalvular leaks are characterized by complex etiology, but in most cases the mechanism of leak development is associated with insufficient contact of the prosthesis to the aortic annulus, prosthesis-patient mismatch, or malap-

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position of the prosthesis. The risk factors for PVL after TAVI can therefore be divided into anatomical factors, factors associated with the clinical characteristics of the patient (patient-dependent factors), and factors associated with the procedure itself (procedure- and operator-dependent factors) [11].

Anatomical and clinical factors

The anatomy of the aortic annulus, which is the device landing zone (DLZ) for both self-expanding and balloon-expandable aortic valve prostheses, plays an important role in the etiopathogenesis of PVL [7, 12]. In contrast to SAVR, it is impossible to directly evaluate the size and shape of the annulus during TAVI. Therefore it is necessary to employ imaging techniques such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), multirow-detector computed tomography (MDCT), aortography, or magnetic resonance [13]. In current clinical practice, two-dimensional TEE is the method most commonly used for annular assessment, but this technique has numerous limitations [5, 14]. Like TTE, TEE enables to evaluate only one dimension of the annulus, which does not always reveal the maximum annular diameter. This may lead to underestimation in contrast to MDCT, which enables three-dimensional (planimetric) evaluation [9, 15-17]. This stems from the fact that presenting the aortic annulus as a circle is a crude approximation. Tops *et al.* reported that in 47% of the studied patients the aortic annulus was oval in shape; i.e., its diameter in the frontal plane was at least 3 mm larger than in the sagittal plane [15]. Planimetric evaluation provides the ability to establish both the longest and shortest diameter, as well as the diameter calculated based on annular circumference or area; thus, it provides more precise information in the case of elliptical aortic annuli. Furthermore, MDCT provides additional information about other anatomical risk factors for PVL occurrence, such as the mass and distribution of calcifications, which confirms the validity of using this imaging method in the evaluation of native valve anatomy [15, 18, 19].

Shape and size of the aortic annulus

The most often used measure of aortic annulus ovality is the annulus eccentricity index (AEI) defined as [1-(the quotient of the shortest and longest diameter of the aortic annulus)] [9, 20-22]. Based on this formula, AEI is equal to 0 for a perfect circle and increases with the rise of annulus ovality [20]. Wong *et al.* demonstrated that AEI correlates strongly with the occurrence of significant paravalvular leaks after the implantation of CoreValve (CV) devices and that, for the assumed AEI cut-off point of > 0.25, it enables to predict PVL occurrence with 80% sensitivity and 86% specificity [22]. These findings were confirmed by Hahn *et al.* who proved that AEI correlates with the PVL grade [23]. However, not all reports on the association between PVL and the oval shape of the annulus are consistent. Marwan *et al.* [24] and Hanson *et al.* [21] did not confirm the association between AEI and the grade of PVL in groups of patients

who were treated with balloon-expandable Edwards-Sapien (ES) valves. The different results may have been related to the used valve type. Balloon-expandable prostheses, characterized by substantial stiffness, retain their circular shape regardless of the anatomy of the aortic annulus [25], stretching the annulus, which is associated with the increase of the shorter annulus diameter and the reduction of the longer one, in effect leading to a significant reduction of AEI after valve implantation [9].

Another well-known risk factor for PVL is the aortic annulus diameter. Risk for PVL rises with increased annulus diameter [13, 26]. This probably explains more frequent occurrence of significant leaks in patients with a large body surface area [23], tall persons [7, 27], and men [5, 23, 27]. The relationship between the size of the annulus and PVL development can most likely be explained by the limited spectrum of valve sizes and the difficulties with selecting adequate valves for patients with larger aortic annuli [27]. Recently, Masri *et al.* used a novel method of evaluating the change of annular shape during the whole cardiac cycle using MDCT with software enabling four-dimensional imaging (three-dimensional projections analyzed over time). They demonstrated that a small difference between the largest and smallest diameter of the annulus evaluated during the whole cardiac cycle (low annulus deformability) significantly predisposes to PVL and TVR after TAVI procedures [28].

LVOT-ascending aorta angle

Sherif *et al.* conducted a study in a group of patients undergoing CV implantation and found a relationship between the occurrence of significant PVL after TAVI and the angle between the left ventricular outflow tract (LVOT) and the first 4 cm of the ascending aorta (AO) [29]. The angle was an independent risk factor for PVL: the risk increased with the rise of the angle width (OR = 1.24). CV device, implanted into the left ventricular outflow tract and reaching into the ascending aorta in patients with large LVOT-AO angles, is exposed to significant tension, which may lead to stent deformation, causing a reduction in the tightness of the paravalvular space [12]. To the best of our knowledge, no study has confirmed the influence of large LVOT-AO angles on the development of AR in patients with ES valves. The design of the latter one is different, and the valves are implanted almost exclusively at the level of the aortic annulus.

Extent and distribution of calcifications

The presence of calcifications on the degenerated native valve is very common in patients with aortic stenosis. It is associated with stenosis progression and occurs, to varied extent, in practically all patients with severe aortic stenosis [15, 30, 31]. It is widely believed that the presence of extensive calcifications in the DLZ precludes complete prosthesis expansion and its precise apposition to the native valve and LVOT, thus favoring the development of PVL. This hypothesis was confirmed by the results of most studies. Delgado *et al.* evaluated the total amount of calci-

fications on the native aortic valves of patients undergoing TAVI using MDCT and calculating the Agatston Calcium Score (AgS) [19]. They demonstrated the presence of a significantly larger calcifications in patients in whom at least moderate AR developed in comparison with patients in whom AR was mild or trivial. A similar relationship between the amount of calcification (evaluated with a semi-quantitative method and AgS) and the degree of AR was demonstrated by Marwan *et al.* in a group of patients with ES valves [24]. A study by Koos *et al.* confirmed these findings and also demonstrated that assuming an AgS cut-off point of > 3000 units predicts the occurrence of significant AR or the need for performing post-dilatation with 86% sensitivity and 70% specificity [32]. There are also other reports confirming the significant relationship between calcification of the valve and the occurrence of leaks [18, 33] as well as the need for post-dilatation in order to optimize the outcome of TAVI [34]. On the other hand, the data from the German registry of 690 patients undergoing TAVI do not confirm the influence of the amount of calcifications on the development of significant leak [5].

The data concerning the influence of calcifications asymmetry and their location in specific DLZ points on the development of PVL are more ambiguous than in the case of the total amount of calcium. Ewe *et al.* discovered that PVL location using echocardiography after TAVI depends on the location of the calcifications; i.e., a PVL is most likely to occur if there is a large volume of calcium at the wall of valve cusp, while the risk is lower if the calcifications are located on the free cusp margins or within the valve cusps. The situation is similar in the case of PVL at the cusps commissures, which is most often associated with calcifications located on the commissures and, to a lesser extent, with the presence of calcification on the free margins of the valve cusps [18]. Other factors related to PVL development included the asymmetric distribution of calcifications [10] as well as the presence of calcifications on individual cusp commissures [19, 33] and within the valve cusps [33]. Some of the studies did not confirm the existence of a relationship between the location and asymmetric distribution of calcifications and the occurrence of PVL and TVR [32, 35, 36]. Substantial differences in the results of the mentioned studies may stem from the use of various methods of evaluating calcification (MDCT, echocardiography), the assumption of various definitions for calcification distribution and asymmetry, as well as relatively small patient groups.

Other anatomical and clinical risk factors for the leak

Apart from the risk factors mentioned above and analyzed by numerous studies, there are a number of factors related to the anatomical and clinical characteristics of patients that have been analyzed by fewer researchers. These factors include the aortic valve area (the larger the area, the smaller the risk of AR) [5, 37], high baseline transvalvular gradient [38], ejection fraction < 30% [5], symptomatic heart failure in NYHA class IV [10], peripheral vascular dis-

ease [26], and other factors for which it is difficult to unequivocally explain their relationship with the etiology of the leak, e.g., renal failure [5]. In turn, leak development has not been shown to be influenced by the size of the sinus of Valsalva or the ascending aorta, i.e. structures belonging to the DLZ that could potentially constitute factors influencing AR [22, 29].

A separate issue is bicuspid aortic valve (BAV), which is a relative contraindication for TAVI [39] even though it occurs relatively often (in about 20% of cases) in the group of patients who are potential candidates for this treatment [39]. Bicuspid valves are more oval in shape, have larger annuli, and are characterized by massive and asymmetric calcifications; therefore they have many features that have been demonstrated to predispose to leak development [40]. Furthermore, the study by Abdel-Wahab *et al.* demonstrated a trend of more frequent AR occurrence in patients with BAV [5]. On the other hand, the most recent studies have shown that AR was not more common in selected BAV patients than in patients with tricuspid valves [41, 42]. However, these data come from relatively small registers, so they do not constitute sufficient evidence for using TAVI routinely in the group of patients with BAV.

Procedural factors

Apart from factors associated with the anatomy and clinical characteristics of the patient, factors associated with procedure also play an important role in leak development. They include, among others, the selection of an appropriate imaging modality for the evaluation of key anatomical parameters of the DLZ as well as the selection of valve type and size. The experience of the center and operators also plays a significant role. Procedural risk factors are especially important for clinicians, because they can potentially be modified in order to limit the occurrence of PVL after TAVI and improve treatment outcomes.

Valve type

The occurrence of PVL may be influenced by the selection of the valve type. In some studies, patients received CV prostheses suffered from significant AR more frequently than patients who received ES valves [37, 43]. Different results were provided by a large British registry encompassing 2584 patients, indicating that the use of balloon-expandable prostheses increases the risk of significant PVL. Moreover, an interesting conclusion of the study was that the postoperative presence of moderate/severe AR had a significant influence on mortality only in the group of patients treated with balloon-expandable valves and not in all patients undergoing TAVI [38]. To the best of our knowledge, there are no other studies confirming this relationship. The introduction to the market of new generations of repositionable valves whose structure increases the tightness between the annulus and the prosthesis raises hopes for reducing the incidence of PVL after TAVI. Especially promising are the outcomes of clinical studies concerning the Lotus valve (Boston Scientific, Marlborough, Massachu-

setts, USA) and the Direct Flow Medical valve (Direct Flow Medical Inc., Santa Rosa, CA, USA). The published results of the clinical REPRISE II study investigating Lotus device, demonstrated that moderate PVL was present in only 1% of patients 30 days after the procedure; in the remaining cases there was no leak or the leak was mild, whereas in study investigating Direct Flow Medical valve only one case of moderate PVL in a group of 74 patients occurred [44, 45]. Perhaps, if the new generation valves enable a significant reduction of PVL occurrence, it will be possible to extend the indications for TAVI to patients with lower surgical risk.

Valve size selection and imaging

The selection of the appropriate size of the prosthesis in relation to the aortic annulus size is one of the key elements of preparing for TAVI procedures. Too small valve prevents the prosthesis from adhering tightly to the annulus, which results from the insufficient transverse force exerted on the aortic valve complex by the prosthesis; thus, it may lead to lack of tightness around the prosthesis and, consequently, to PVL [7, 46]. In turn, implanting a valve that is too large may cause such complications as annulus rupture or coronary artery occlusion [7, 9]; notwithstanding, in order to minimize the risk of PVL, the use of valves that are slightly oversized is recommended [47]. One of the most important risk factors for PVL is the cover index (CI), which depends on the size of the prosthetic valve and the aortic annulus and is defined by the following formula: $[100 \times (\text{external diameter of the prosthetic valve} - \text{aortic annulus diameter}) / \text{external diameter of the prosthetic valve}]$ – the lower the CI value, the higher the risk [7, 20]. Détain *et al.* observed that, in their group of patients with balloon-expandable valves, significant PVL never occurred when CI was $> 8\%$ [7].

The proper annulus evaluation plays the key role in the selection of valve size. As mentioned above, the annulus diameter established on the basis of two-dimensional TEE may be underestimated. To the best of our knowledge, there have been no randomized studies comparing the incidence of PVL in patients whose aortic annuli were assessed with two-dimensional TEE and MDCT. A retrospective study by Mylotte *et al.* demonstrated that 50% of patients would have been provided with CV valves of inadequate size (inconsistent with current recommendations) if the selection had been based on the annulus size established by TEE examination. Moreover, the authors reported that the selection of the recommended valve size based on MDCT measurements enables to achieve a 20% reduction of the incidence of significant PVL [46].

The incidence of this complication can also be minimized by using the optimal (coplanar) fluoroscopy projections, which facilitates proper valve positioning and implantation [48].

Other procedural risk factors for PVL

The depth of implantation appears to be a predictive factor for PVL that is characteristic of the CV device. In contrast to the ES valve, which can only be implanted in

a narrow range of depths, the CV device has high profile and that can be placed at a wider range of depths [29]. However, if the valve is implanted too deep (low), this can result in a leak through the stent cells, as its structure is covered with porcine pericardium only in the lower part of the prosthesis [49]. Sherif *et al.* established that the optimal implantation was performed when depth of the device in relation to the noncoronary cusp was ~ 10 mm.

Implanting the valve in a lower or higher position was associated with higher grade of AR [29]. In turn, in a study by Takagi *et al.*, low valve implantation (≥ 3 stent cells below the valve annulus) was an independent risk factor for significant PVL (OR = 3.67) [26].

The experience of the center and operator performing TAVI also affects the outcome. The influence of the learning curve on AR incidence has been clearly demonstrated; the incidence is falling with growing number of performed procedures [7, 50].

Conclusion

Paravalvular leak is currently one of the most significant problems connected with TAVI procedures. There are many factors known to predict the occurrence of this complication. Understanding these factors may improve the assessment of risk and the selection of more personalized treatment. The increasing number of TAVI performed around the world, the optimization of procedures based on data from large clinical studies, and the introduction of new technologies associated with prosthetic valves and imaging methods offer a chance for a substantial reduction in the incidence of significant PVL, thus improving the prognosis of patients undergoing TAVI.

Disclosure

Authors report no conflict of interest.

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