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Clinically relevant haemolysis after transcatheter aortic valve implantation with new-generation balloon-expandable valve

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ABSTRACT

Background Valve-related haemolysis is a known complication following prosthetic valve surgery. Haemolysis after transcatheter aortic valve implantation (TAVI) has been reported in some studies, all of which were non-critical. Data related to haemolysis associated with new-generation balloon-expandable valve (BEV) are scarce.

Methods Among 441 patients who underwent TAVI between April 2023 and June 2024, 282 patients treated with new-generation BEV were analysed. Haemolysis was defined based on the lactate dehydrogenase, haemoglobin, reticulocyte and haptoglobin levels. Clinically relevant haemolysis was defined as a case requiring transfusion and/or reintervention.

Results Clinically relevant haemolysis occurred in 6 of 282 patients (2.1%), with median age of 84 years. Three (50%) received a 20 mm valve, and the oversizing ranged from −6.6% to +2.7%. All patients (100%) exhibited paravalvular leakage at the native commissural sites, with moderate or greater paravalvular leakage in two (33%). Lactate dehydrogenase levels exceeded 1200 IU/L in five (83%), four (67%) required transfusion and three (50%) underwent reintervention: balloon aortic valvuloplasty in one and valve-in-valve procedures in two. Haemolysis regressed in three reintervention cases; however, one patient died 9 days postoperatively due to COVID-19. Among three patients (50%) managed conservatively, one developed prosthetic valve endocarditis, whereas another showed spontaneous regression of haemolysis. Over a median follow-up of 218 days, five patients (83%) survived.

Conclusion Clinically relevant haemolysis occurred in 2.1% of patients undergoing TAVI with new-generation BEV, with 67% requiring transfusion and 50% undergoing reintervention. Further research is warranted to identify risk factors and optimise management strategies for haemolysis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Valve-related haemolysis can occur in both surgical and transcatheter aortic valves, most of which are subclinical without transfusion or reintervention.

WHAT THIS STUDY ADDS

⇒ Clinically relevant haemolysis with transfusion and/or reintervention was detected in 2.1% of 282 transcatheter aortic valve implantations with the new-generation balloon-expandable valve.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The incidence, causes and management of clinically relevant haemolysis should be further investigated in a larger population.

INTRODUCTION

Haemolysis can occur after surgical valve replacement, being reported in 18%–51% of the current generation bileaflet mechanical valves and 5%–10% of bioprosthetic valves.[1 2] Risk factors for haemolysis include paravalvular leakage (PVL), prosthesis–patient mismatch, structural valve deterioration and endocarditis. Most cases of haemolysis patients are subclinical, and a few patients experience decompensated haemolysis. Haemolysis has occurred in 9%–28% of transcatheter heart valves, including both balloon-expandable valves (BEVs) and self-expanding valves, all of which were non-critical.[3–5] A new-generation BEV, SAPIEN3Ultra RESILIA (S3UR) (Edwards Lifesciences, Irvine, California, USA), was approved in Japan in February 2023 and in the USA in July 2022. The S3UR features the ultra skirt to reduce PVL and the RESILIA tissue leaflet to prevent valve calcification compared with the former BEV, SAPIEN3 valve (Edwards Lifesciences).[6] There is a paucity of data on haemolysis caused by S3UR. We sought to evaluate clinically relevant haemolysis with the S3UR.

METHODS

Study design and participants

This study was a single-centre, retrospective, observational study. Among 441 consecutive patients undergoing transcatheter aortic valve implantation (TAVI) between 3 April 2023 and 31 July 2024, we analysed 282 patients using S3UR via the medical records and a dedicated database (online supplemental figure 1).

TAVI procedures

In general, TAVI is performed under local anaesthesia with deep sedation and transthoracic echocardiography guidance. Here, the valve was implanted using the radiolucent line technique,[7] and the size was selected based on the manufacturer's chart. In patients with a borderline annulus size, the valve was selected based on aortic root size, extent of leaflet calcification and individual life expectancy. The PVL was assessed using transthoracic echocardiography and aortography after valve deployment. Blood tests, including haemoglobin, total bilirubin and lactate hydrogenase (LDH), were performed on the same day, the next day and thereafter at the discretion of the treating physician. Red blood cell transfusion was considered in cases with haemoglobin less than 80 g/L or symptomatic anaemia of 80–100 g/L. Reintervention procedure was determined by the heart team discussion, taking into account the degree of aortic regurgitation, the need for transfusion and heart failure symptoms.

Outcome measures

Haemolysis was defined according to the Skoularigis criteria without shistocytes.[4] Clinically relevant haemolysis was defined as haemolysis requiring red blood cell transfusion and/or reintervention. Considering the probability of underreporting non-clinically relevant haemolysis due to the nature of daily clinical practice, we extracted only cases with clinically relevant haemolysis occurring after TAVI. The per cent oversize was calculated as [(nominal S3UR area/annulus area)−1]×100 (%).

Statistical analysis

Categorical variables were presented as counts with percentages, and continuous variables as median values or total ranges. Due to the limited number of patients with clinically significant haemolysis, statistical group comparisons and risk factor analyses were not performed.

RESULTS

Baseline and procedural characteristics

Among 282 patients undergoing TAVI with S3UR, clinically relevant haemolysis was observed in 6 patients (2.1%) with severe tricuspid aortic stenosis (online supplemental tables 1 and 2). The median age was 84 years with four (67%) being female. A 20 mm valve was used in three patients (50%), and the per cent oversizing ranged from −6.6% to +2.7%. Furthermore, there were no cases of prosthesis–patient mismatch. All patients exhibited some PVL corresponding to the native valve commissure, especially at 2 and 10 o'clock, and two of them (33%) were moderate or greater grade. The maximum LDH level during follow-up was greater than 1200 IU/L except in case 5. Four patients (67%) required transfusion, and three patients (50%) underwent reintervention, including balloon aortic valvuloplasty (BAV) in one (17%) and redo TAVI in two patients (33%). Among three patients (50%) managed conservatively, one developed prosthetic valve endocarditis (case 6), while another showed spontaneous regression of haemolysis (case 3). Over a median follow-up of 218 days, five patients (87%) were alive.

Case 1

Case 1 involved a mid-80s male patient with end-stage renal disease and cirrhosis. A 23 mm S3UR valve was deployed at a high position (figure 1A). Moderate PVL was observed at 2 and 10 o'clock with haemolytic anaemia (figure 1B,C). The patient developed acute pulmonary oedema 1 week after TAVI. However, redo TAVI could not be performed because of leaflet thrombus at the non-coronary cusp (figure 1D,E). Anticoagulation with unfractionated heparin was implemented but discontinued because of intestinal bleeding. Immediately after 3 weeks of hospitalisation, the patient was readmitted for refractory heart failure. Furthermore, leaflet thrombus persisted with severe thrombocytopaenia of 10×10^3/μL. After regression of the leaflet thrombus using deliberate unfractionated heparin with haptoglobin and platelet concentrate supplementation, redo TAVI was performed with a 23 mm S3UR valve (figure 1F,G). The PVL regressed from moderate to mild grade (figure 1H) with a decrease in LDH from 1367 to 906 IU/L. However, the patient succumbed 9 days after TAVI due to COVID-19.

Case 2

Case 2 involved an early-80s female patient with an annulus of 346 mm^2, and a 20 mm S3UR was deployed at a high position (figure 2A). The PVL was mild grade at the 5 and 10 o'clock positions, with mild haemolysis of 400–600 IU/L of LDH for 6 months (figure 2B). At the 1-year follow-up, haemoglobin level decreased from 123 to 90 g/L with elevated LDH of 1246 IU/L. As the PVL deteriorated to a moderate to severe grade (figure 2C–E), we performed BAV with provisional TAVI. Since BAV with a 20 mm balloon was ineffective, a 20 mm S3UR was deployed 5–6 mm lower (figure 2F). The PVL regressed to a trivial grade (figure 2G,H), and the LDH level decreased to 768 IU/L 1 week after TAVI.

DISCUSSION

Prevalence and pathophysiology of valve-related haemolysis

Valve-related haemolysis primarily occurs through two mechanisms: high shear stress and direct collision between erythrocytes and the surrounding structures.[2] Surgical prosthetic valve-related haemolysis has been the subject of extensive investigation; however, haemolysis

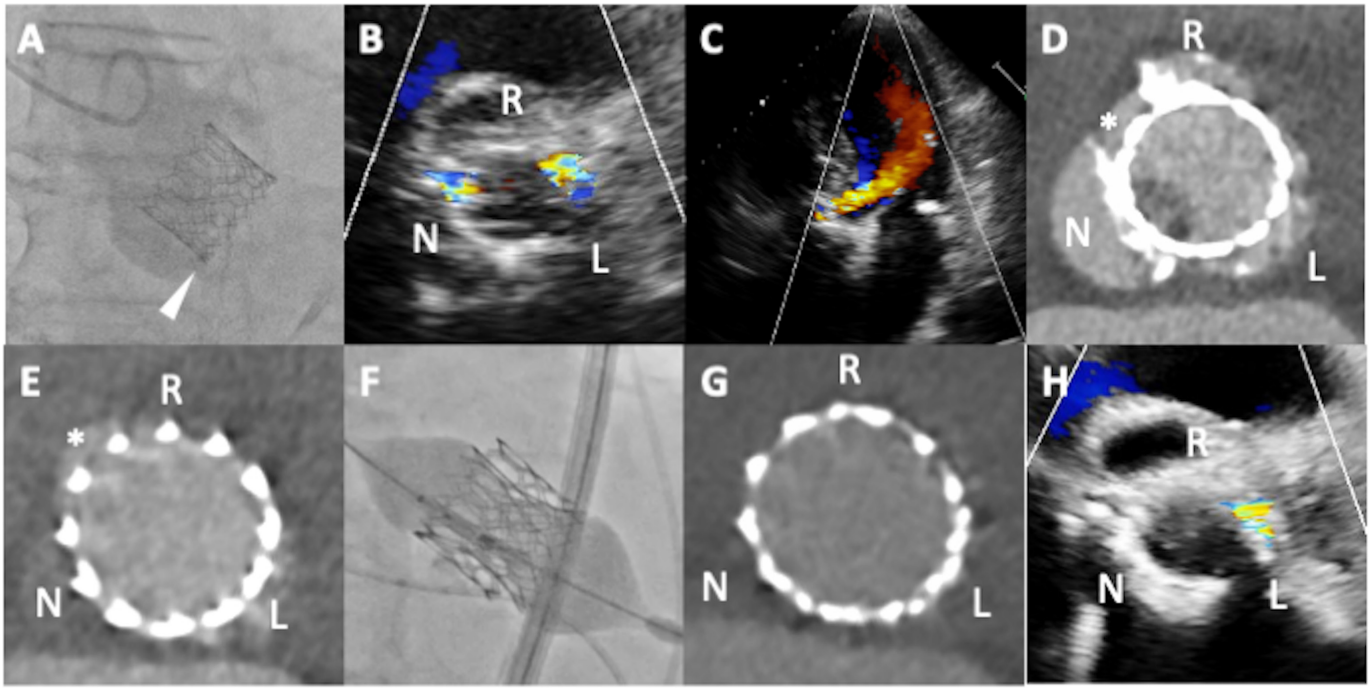

Figure 1 Paravalvular leakage (PVL) in case 1 (A) aortography after valve deployment, (B, C) PVL observed after transcatheter aortic valve implantation (TAVI), (D, E) CT imaging after the initial TAVI, (F) redo TAVI, (G) CT imaging after redo TAVI, (H) PVL observed after redo TAVI. R: right-coronary cusp; L: left-coronary cusp; N: non-coronary cusp; arrowhead: nadir of the non-coronary cusp; asterisk: interspace.

resulting in significant anaemia is rare in the absence of valve malfunction. The most common cause of valve-related haemolytic anaemia is PVL, which is the so-called Achilles tendon of the transcatheter aortic valve (TAV). The incidence of mild or greater PVL remains higher in TAVs than in surgical aortic valves.[8 9] Moreover, the extent of haemolysis does not necessarily correlate with the severity of PVL. The occurrence of haemolysis after TAVI

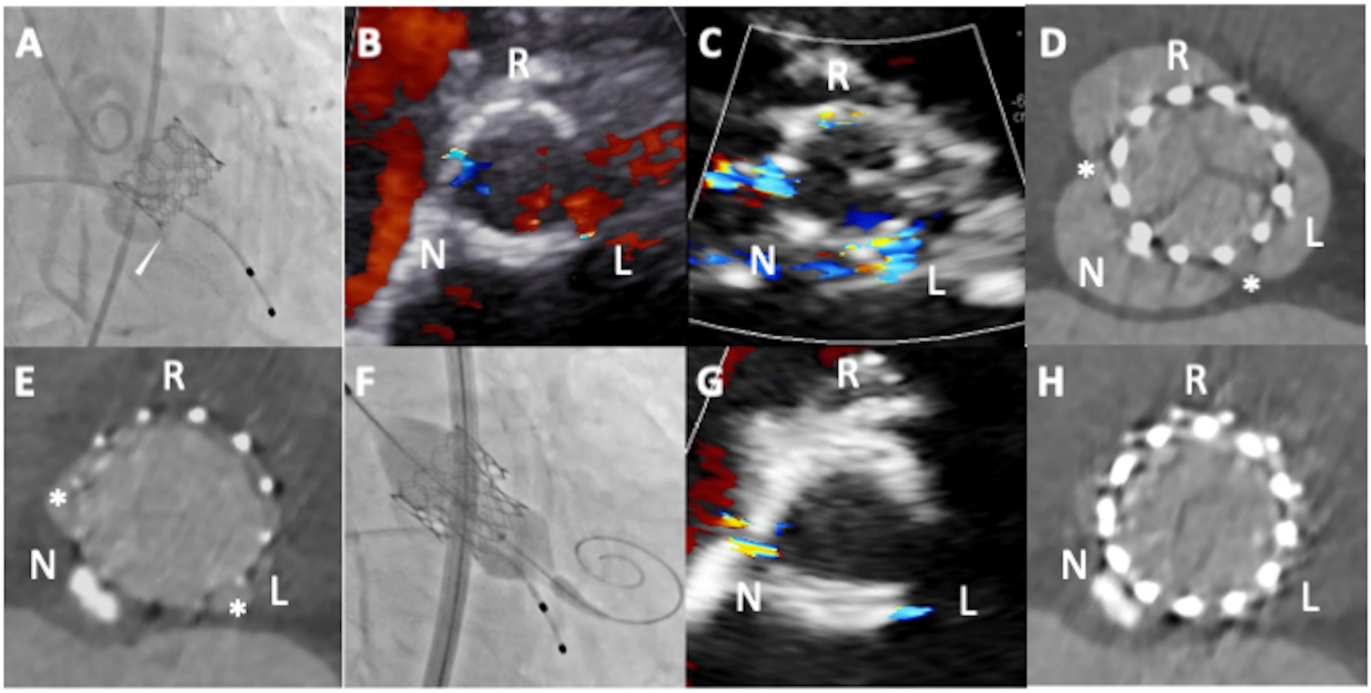

Figure 2 Paravalvular leakage (PVL) in case 2 (A) aortography after valve deployment, (B, C) PVL observed immediately and 1-year post-transcatheter aortic valve implantation (TAVI), (D, E) CT imaging after the initial TAVI, (F) redo TAVI, (G) PVL observed after redo TAVI, (H) CT imaging after redo TAVI R: right-coronary cusp; L: left-coronary cusp; N: non-coronary cusp; arrowhead: nadir of the non-coronary cusp; asterisk: interspace.

is 9%–28%, including both BEVs and self-expanding valves.[3–5]

For example, Laflamme *et al* reported haemolysis in 18 of 122 patients (14.8%), the majority of whom (115/122) received BEVs.[3] Patients with haemolysis showed a higher prevalence of patient–prosthesis mismatch, increased wall shear rates and a lower energy loss index. Similarly, Ko *et al* observed haemolysis in 14 of 64 patients (21.9%), with most (93.8%) treated with self-expandable or mechanically expandable valves.[4] In their multivariate analysis, bicuspid aortic valve and moderate or greater PVL were identified as independent risk factors for haemolysis. Širáková *et al* investigated 94 patients who underwent TAVI with self-expanding valves.[5] No clinically significant haemolysis cases were observed in these studies. Interestingly, in the present study, clinically relevant haemolysis was identified in 2.1% of cases. The oversizing ratio is associated with the occurrence of PVL, and the per cent oversizing in our six patients was relatively low (−6.6% to +2.7%).[10] Six patients (100%) with haemolysis also demonstrated PVL at the native valve commissures, especially at the 2 and/or 10 o'clock positions. Modest oversizing and high-valve implantation using the radiolucent technique may cause significant PVL at the commissures. Four patients (67%) exhibited worsening PVL; however, the underlying causal relationship remains uncertain. Possible reasons for clinically relevant haemolysis being observed exclusively in the present study may include differences in valve type, procedural plan, patient characteristics and postprocedural follow-up.

Management of valve-related haemolysis

A total of three patients (1.2%) required reintervention in the present study. Management options for TAVI-related haemolysis include medical therapy, BAV, redo TAVI (ie, TAV-in-TAV), explant surgery and transcatheter PVL closure.[1 2] According to the European Society of Cardiology guideline, reoperation is recommended in cases of repeated transfusions and refractory heart failure.[11] The explant of TAV is a high-risk surgical procedure, and the decision to proceed with or without explant should be made solely based on the particular case. Transcatheter PVL closure is a potential alternative therapy, but as of November 2024, it is approved only for cases involving surgical prosthetic valves in Japan. Although transcatheter PVL closure was effective for heart failure related to haemolysis in the PLUGinTAVI registry, residual mild or greater aortic regurgitation was identified in 71% of cases, which may result in haemolysis.[12] Theoretically, BAV would be effective for cases with valve underexpansion or recoil but may be ineffective for high valve implantation. A redo TAVI would be the preferred option for cases with high valve implantation but with a risk of sinus sequestration and the complexity of a third-do procedure (ie, TAV-in-TAV-in-TAV).[13] Both options carry the potential risk of aortic root injury in patients with calcified valve leaflets. Here, the initial valves were highly implanted in cases 1 and 2, and the TAV-in-TAVs performed were effective in both cases.

Study limitations

First, this study was a single-centre, retrospective study. The incidence of haemolysis may be affected by the types of valves and procedures involved. Moreover, the absence of a systematic follow-up protocol precluded a thorough assessment of the occurrence of non-clinically relevant haemolysis. Second, the sample size was limited, necessitating further analysis to ascertain the incidence, mechanism and outcome of TAVI-related haemolysis.

CONCLUSIONS

Clinically relevant haemolysis was observed in 6 of 282 patients (2.1%) undergoing TAVI with new-generation BEV. In all cases, haemolysis was accompanied by PVL, corresponding to the native valve commissures. Among the patients who experienced haemolysis, four (67%) received transfusion, and three (50%) underwent reintervention. The remaining cases included one instance of prosthetic endocarditis and another wherein the haemolysis spontaneously resolved. Five patients (87%) survived over a median 218 days follow-up. In order to identify the risk factors and optimise management strategies for haemolysis, further research should be carried out in the future.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Sakakibara Heart Institute, 17-005. Participants gave informed consent to participate in the study before taking part.

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The data underlying this article will be shared on reasonable request and with the approval of the relevant ethical committee.

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