Hypo-attenuated leaflet thickening of transcatheter aortic valves: jeopardy or epiphenomenon?

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Abstract

This editorial refers to ‘Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke’, by E.M. Vollema et al., on page 1207.

In this issue of the journal, Vollema et al. shed new light on the phenomenon of hypo-attenuated leaflet thickening (HALT) with transcatheter aortic valve prostheses.1 In context of the important new data they report, this Editorial intends to revisit the potential haemodynamic and clinical relevance of HALT.

HALT: a new phenomenon of unknown relevance

HALT has been reported as a mostly incidental finding on multislice computed tomography (MSCT) angiography.1-5 It is characterized by lesions with lower density above the leaflets of the prostheses and in most cases is associated with restricted leaflet motion.1,4 The consistent finding of resolution of HALT under oral anticoagulation suggests thrombosis as the underlying mechanism.2-5 Reported incidences of HALT range around 10% after transcatheter aortic valve implantation (TAVI).2-4 HALT may occur with any type of transcatheter aortic valve and has also been reported with surgical valve prostheses.2-5 In surgically implanted prostheses, valve thrombosis is a dreaded complication. Based on earlier experience in this setting, it is associated with valve dysfunction as well as increased risk of thrombo-embolic events and ultimately death.6,7 Yet, unlike HALT that is unusually a chance finding in asymptomatic patients, detection of valve thrombosis in the earlier studies on surgical valves was always triggered by clinical symptoms.6,8 Moreover, modern CT technology enables the detection of minute changes in leaflet structure and motion that cannot be detected by any other method and, therefore, is not represented in the earlier literature on surgical valves.2 Hence, there is reasonable doubt about the clinical relevance of HALT.

So far, published data on the clinical course of patients with HALT are limited: the largest data sets by Makkar et al., Pache et al., Hansson et al., and Yanagisawa et al. included only 39, 16, 28, and 10 patients, respectively.2-4,9 Moreover, looking at the impact of antithrombotic treatment, Ruile et al. extended the series of Pache et al. to 51 patients.2 In the previous studies, clinical follow-up was limited to 1 year.2-5,9 It is the merit of the current study by Vollema et al. to report clinical and echocardiographic follow-up for up to 3 years in 16 patients with HALT out of a subset of 128 patients with MSCT after TAVI.1 To corroborate their clinical findings in patients with HALT, they also assessed the clinical course of 13 patients who met the echocardiographic criteria for valve thrombosis within the entire cohort of 431 patients with TAVI.

When assessing the clinical relevance of HALT, two key issues need to be addressed: the impact of HALT on valve function and the risk of thrombo-embolic events.

Impact of HALT on valve function (Table 1, Figure I)

At the time of MSCT, Pache et al. and Hansson et al. reported significantly higher transvalvular gradients across prostheses with HALT as compared with prostheses without HALT (14.9 ± 5.3 vs. 11.6 ± 3.4 mmHg, P = 0.026, and 10 ± 7 vs. 8 ± 3 mmHg, P = 0.003, respectively).2,4 Similar results were reported for valves in the PORTICO study by Makkar et al. (10.5 ± 4.3 vs. 9.0 ± 4.9 mmHg, P = 0.10).1 In the other valves reported by Makkar et al. and in the valves reported by Yanagisawa et al., there was no difference in transvalvular gradients between valves that subsequently or previously developed HALT.
<table>
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<tr>
<th>Table 1</th>
<th>Reports on HALT with transcatheter aortic valve prostheses</th>
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<tr>
<td>---------------------------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>Patients with HALT, n (% of patients with MSCT)</td>
<td>22 (37%)</td>
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<tr>
<td>Transvalvular gradient at time of MSCT, HALT vs. no HALT</td>
<td>10.5 ± 4.3 vs. 9.0 ± 4.9 mmHg, P = 0.10</td>
</tr>
<tr>
<td>Change in transvalvular gradients during follow-up</td>
<td>No (some patients switched to AC)</td>
</tr>
<tr>
<td>Valve haemodynamic deterioration, n (% of patients with HALT)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke during follow-up, n (% of patients with HALT)</td>
<td>0</td>
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AC, anticoagulation; HALT, hypo-attenuated leaflet thickening; MSCT, multislice computed tomography.
and those that did not.3,9 Yet, the data are difficult to interpret as the timing of echocardiographic studies with respect to the occurrence of HALT is unclear. Supporting an impact of HALT on transvalvular gradients, the study of Vollema et al. also shows higher transvalvular gradients with HALT at the time of MSCT with marginal statistical significance ($P = 0.056$).1 Nevertheless, the average differences in gradients between valves with and without HALT reported thus far are minimal.1–5 There was, however, a broad variability in the extent of HALT as well as in transvalvular gradients, and 1 out of 24 patients of the study by Hansson et al. and 1 out of 16 patients of the current study by Vollema et al. met the criteria for valve haemodynamic deterioration (VHD; increase of mean transvalvular gradient to >20 mmHg) already at the time of MSCT.1,4

There has been concern that HALT may progress, if the antithrombotic regimen is left unchanged. In this respect, Vollema et al. present important data in showing that transvalvular gradients in valves with HALT increased marginally with time and that the differences in valve area and transvalvular gradient between patients with and without HALT increase during the first 6 months after diagnosis by MSCT (6-month data for patients with vs. without HALT: 1.32 ± 0.35 cm² vs. 1.76 ± 0.49 cm², $P < 0.01$, and 12.4 ± 8.0 mmHg vs. 9.4 ± 4.3 mmHg, $P = 0.026$, respectively). Nevertheless, no additional patient developed VHD. Some of the previous studies were difficult to interpret with respect to progression to transvalvular gradients. Patients were systematically put on anticoagulation in the study by Pache et al. and, in the studies of Makkar et al. and of Hanson et al., some, but not all patients were switched from pure antiplatelet therapy to anticoagulation.2–4 It is, however, noteworthy that in the study by Hansson et al., four additional patients with HALT, all without anticoagulation, acquired VHD during follow-up.4

Additional evidence for a potential progression of HALT under standard antiplatelet therapy comes from the study of Ruile et al.5 In this study with a second MSCT after 3 months, HALT progressed in 11 of 16 patients on dual antiplatelet therapy, but always regressed in 22 patients on anticoagulation. The change in mean transvalvular pressure gradient differed significantly between the two treatment regimens ($P = 0.012$): With dual antiplatelet therapy, gradients increased by trend ($Δ3.57 ± 6.52 mmHg$, $P = 0.061$) and one patient developed VHD. In contrast, in the group under anticoagulation, a numerical average decrease ($Δ−1.98 ± 5.66 mmHg$, $P = 0.125$) was found. In the entire group, changes in leaflet restriction, thrombus extent, and maximum thickness correlated significantly with the change in maximal pressure gradient ($P = 0.010$, 0.017, and 0.037, respectively).

Thus in most cases HALT does not cause a clinically relevant increase in transvalvular gradients. Bench testing by the group of Makkar et al. revealed that even complete blockage of the motion of one leaflet was not associated with a relevant increase in transvalvular gradients.3 Major increases in transvalvular gradients were only seen with blockage of two leaflets. In the clinical setting, a comparable leaflet restriction by HALT is rare, but may occur exceptionally. In the rare cases of extensive HALT causing VHD, it is reassuring that in the limited experience thus far, HALT has always been reversible under anticoagulation.2–5

### Impact of HALT on thrombo-embolic events (Table 1, Figure I)

In the study by Hanson et al., two strokes occurred during 1-year follow-up in 17 patients with HALT and eight strokes in 229 patients without HALT (12% vs. 3%, $P = 0.15$).7 All other studies did not...
report any stroke or any other thrombo-embolic event in patients with HALT during follow-up periods of up to 1 year.\textsuperscript{3,13,19} Nevertheless, due to the low numbers of patients included and the variable treatment regimens, uncertainty remained.

In the current study by Vollema et al. with a follow-up of up to 3 years, the investigators also did not encounter any stroke in 16 patients with HALT, and the same was true for the 13 patients with echocardiographic criteria for valve thrombosis.\textsuperscript{1} Nevertheless, the numbers of patients included were still low—considering that stroke is a relatively rare event and follow-up was incomplete. Thus, the study by Vollema et al. adds additional data suggesting that HALT does not increase the risk of thrombo-embolic events, but cannot provide definite proof.

**Consequences for medical management**

In randomized trials comparing surgical and transcatheter bioprosthetic valves in aortic position, patients with transcatheter valves fared as well or even better than patients with surgical valves.\textsuperscript{10–12} Specifically, none of these studies suggested an increased risk of stroke or other thrombo-embolic events with transcatheter heart valves during long-term follow-up. Moreover, transcatheter valves consistently achieved more favourable transvalvular gradients than surgical valves, with follow-up periods of up to 5 years as in the PARTNER 1A trial.\textsuperscript{13} Thus, there is no rationale that the reports on HALT with surgical aortic valves.

Although currently available evidence suggests favourable sustainability of both transcatheter and surgical valves, a residual small risk of symptomatic valve thrombosis prevails. In an earlier study, the respective incidence within 2 years from transcatheter aortic valve implantation was 0.61%.\textsuperscript{14} Moreover, a recent retrospective analysis from a large TAVI registry found relevant increases in transvalvular gradients of > 10 mmHg in 4.8% of the patients.\textsuperscript{15} This event was less common in patients on anticoagulation as compared with those without, suggesting a role for leaflet thrombosis. Optimizing clinical management with respect to the prevention or treatment of leaflet thrombosis may, therefore, improve the outcome of both transcatheter and surgical bioprosthetic valves. Large-scale clinical trials assessing this issue are underway.

Until the results of these trials become available, the key questions are whether HALT that does not lead to a relevant increase in transvalvular gradients deserves medical attention and whether we should actively search for it. Based on currently available evidence including the new evidence presented in this issue of the journal, we believe the answer is no. In most patients, HALT appears to be innocent, and in the very few that develop VHD HALT still appears to be reversible under anticoagulation. Thus, prudent echocardiographic surveillance may suffice. In those patients, however, who show relevant increases in transvalvular gradients, current knowledge suggests searching for HALT and, if present, treating it as the probable underlying cause for valve deterioration.

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**References**


