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Intraoperative hypotension and delirium among older adults undergoing transcatheter aortic valve replacement

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Abstract

Background: Postoperative delirium (POD) is a frequently observed complication after transcatheter aortic valve replacement (TAVR). The effects of intraoperative hypotension (IOH) on POD occurrence are currently unclear.

Methods: A retrospective observational cohort study of patients who underwent TAVR was conducted. We predefined IOH as area under the threshold (AUT) of five mean arterial blood pressures (MBP), varying from <100 to <60 mmHg. The AUT consisted of the combination of duration and depth under the MBP thresholds, expressed in mmHg*min. All MBP AUTs were computed based on the complete procedure, independent of procedural phase or duration.

Results: This cohort included 675 patients who underwent TAVR under general anesthesia ($n = 128$, 19%) or procedural sedation ($n = 547$, 81%). Delirium occurred mostly during the first 2 days after TAVR, and was observed in $n = 93$ (14%) cases. Furthermore, 674, 672, 663, 630, and 518 patients had at least 1 min intraoperative MBP <100, <90, <80, <70, and <60 mmHg, respectively. Patients who developed POD had higher AUT based on all five MBP thresholds during TAVR. The penalized adjusted odds ratio varied between 1.08 (99% confidence interval [CI] 0.74–1.56) for the AUT based on MBP < 100 mmHg and OR 1.06 (99% CI 0.88–1.28) for the AUT based on MBP < 60 mmHg.

Conclusions: Intraoperative hypotension is frequently observed during TAVR, but not independently associated with POD after TAVR. Other

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potential factors than intraoperative hypotension may explain the occurrence of delirium after TAVR.

KEYWORDS
delirium, intraoperative hypotension, TAVR, transcatheter aortic valve replacement

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has emerged as a valuable option to treat symptomatic severe aortic valve stenosis in older adults considered to be inoperable or at increased risk for surgical aortic valve replacement.[1,2] Compared with surgical replacement, TAVR is a less invasive treatment strategy that is performed on a beating heart without involvement of cardiopulmonary bypass, or sternotomy.[3] Relief of aortic valve stenosis by TAVR is associated with short and mid-term favorable cardiac, hemodynamic and geometrical changes, including improvement of coronary microvascular function, increase in cardiac output and cerebral blood flow, and decrease in interventricular septum and posterior wall thickness.[4–7] Despite improvement in procedural techniques, minimalistic transfemoral approach, and reduced procedural complications rate, the occurrence of postoperative delirium (POD) remains an important complication after TAVR.[8]

Delirium is a clinical expression of acute encephalopathy with a multifactorial etiology and impaired outcome.[9] The reported frequency of POD following TAVR ranges from 10% to 44% depending on the access strategy.[10–13] Clinical adverse outcomes associated with POD after TAVR include prolonged hospital stay, increased readmission rate, and early and long-term post-discharge mortality.[8,10–15]

Delirium is a multifactorial syndrome due to predisposing and precipitating factors. The pathophysiology of POD after TAVR is not well understood, and intraoperative hypotension (IOH) is presumed to play a role.[16–18]

Patients during TAVR experience IOH and cerebral hypoperfusion due to temporary reduction in cardiac output, particularly during valve deployment. For instance, few studies have shown reduction in cerebral oxygenation during TAVR using near-infrared spectroscopy.[19–22] However, the literature on the association of IOH with delirium after TAVR is limited, and heterogeneous with regard to study populations and IOH definitions.

With the increasing number of TAVR procedures, and expanding indications toward patients with lower surgical risk, understanding the etiologies of delirium is crucial to be able to apply preventive strategies. The aim of this study was to investigate the association between IOH and POD after TAVR.

Key Points

- Intraoperative hypotension is frequently observed during TAVR, but not independently associated with POD after TAVR.
- Other potential factors than intraoperative hypotension may explain the occurrence of delirium after TAVR.

Why Does this Paper Matter?

In light of increasing number of TAVR procedures with expanding indications toward patients with lower surgical risk, it is crucial to understand the role of additional procedural factors such as intraoperative hypotension on the development of delirium following TAVR.

METHODS

Design and study population

For this retrospective cohort study, consecutive patients were included who underwent TAVR between August 26, 2008, and March 29, 2018 at the University Medical Center Utrecht, Utrecht, the Netherlands. The need to obtain informed consent for the current study was waived by the Institutional Review Board (identifier 18-287/C). Baseline, clinical, and procedural characteristics were derived from the dedicated local TAVR registry and the electronic medical records.

Preoperative data

Demographic, preoperative, and surgical data were collected from the electronic hospital information system (HiX, ChipSoft, Amsterdam, the Netherlands). Frailty was assessed by an interventional cardiologist and/or cardiothoracic surgeon based on informal 'eyeballing' (including cognition function, physical weakness, and walking speed). Atrial fibrillation at baseline was defined as a history of atrial fibrillation before TAVR or as the presence of atrial

fibrillation on hospital admission. Peripheral artery disease was defined as claudication and/or a history of peripheral surgery and/or angioplasty, and/or stenosis of ≥50% of the iliofemoral axis, which was assessed prior to TAVR by multislice computed tomography. Carotid artery disease was defined as prior or planned carotid artery intervention and/or ≥50% diameter stenosis of the common carotid artery evaluated by computed tomography angiography or duplex investigation.

TAVR procedure

All patients had been judged inoperable or at high operative risk by at least one interventional cardiologist and one cardiac surgeon. Motivations to refuse surgical aortic valve replacement in patients were as follows: (1) logistic EuroSCORE ≥15%,[23] or (2) the presence of contraindications to cardiac surgery.

All transfemoral procedures involved a fully percutaneous technique. Local anesthesia of the access sites was performed by lidocaine infiltration. Procedural sedation was the default method in transfemoral procedures. In non-transfemoral TAVR procedures general anesthesia was applied. For the transfemoral approach, procedural sedation was established by infusion of the sedative propofol (0.4–0.75 mg/kg/h) and the analgesic remifentanil (1.5–3 μg/kg/h). General anesthesia was also initiated and maintained with propofol and remifentanil. The level of intraoperative procedural sedation was frequently assessed according to the Ramsay sedation scale and was maintained between 3 and 5.[24] Intraoperative hypotension was typically treated with fluids, norepinephrine, phenylephrine, or ephedrine at the discretion of the anesthetist.

Intraoperative hypotension

Intraoperative data from the patient monitor and anesthesia machine were stored as the median for each minute of collected data in the electronic anesthesia information management system (AnStat®, CarePoint Nederland BV, Ede, the Netherlands). Mean arterial blood pressures (MBP) of both invasive and noninvasive measurements were extracted. If invasive intra-arterial blood pressures were not available at any time point, oscillometric noninvasive blood pressure measurements were used instead when available. Missing blood pressure data were imputed based on a weighted average of a linear slope component (slope from last available blood pressure measurement to the next available measurement).[25] The following values were considered artifacts and were removed prior to the analyses: diastolic pressure < 20 mmHg or > 200 mmHg, MBP < 0 mmHg and systolic blood pressure < 30 mmHg and > 300 mmHg.

As there is no generally accepted definition of IOH, we predefined IOH as area under the threshold (AUT) of five MBP thresholds (100, 90, 80, 70, and 60 mmHg). The AUT consisted of the combination of duration and depth under these MBP thresholds, expressed in mmHg min, for example, an MBP of 50 mmHg during 5 min corresponds to an AUT of $10 \times 5 = 50$ mmHg min when the threshold was set to a MBP < 60 mmHg. All MBP thresholds were applied during the complete procedure, independent of procedural phase.

Postoperative delirium

The main outcome of this study was the presence of POD during inhospital stay after TAVR. Description of signs of both hypoactive, hyperactive, and mixed delirium in patients' records were reviewed using a protocol based on the diagnostic features of delirium in the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5).[26] A delirium observational score (DOS) was rated at the end of every shift by a trained nurse or attending physician according to the local protocol.[27] This way, further evolution (signs) of delirium could be monitored. POD was defined as DOS ≥3 and/or a combination of the clinical features. The timing of onset of the delirium was also reviewed.

Potential confounders and missing variables

Based on previously performed studies and clinical experience, the following possible confounders were selected a priori: age (years), sex, EuroSCORE,[23,28] preoperative frailty (yes/no), preoperative atrial fibrillation (yes/no), approach (transapical/transfemoral), balloon expandable aortic valves (yes/no), type of anesthesia (general anesthesia/procedural sedation), and duration of the procedure (minutes). No potential effect modifiers were defined a priori, nor analyzed.

Missing values (except blood pressure data and outcome) were imputed through multiple imputation ($n = 20$ datasets) using predictive mean matching "rms ("aregImpute" function, "rms"-package release 5.1-3.1 in R release 3.5.1; R foundation for Statistical Computing, Vienna, Austria). All variables listed in Table 1 were used during the multiple imputation strategy. Missing blood pressure data were imputed based on a weighted average

TABLE 1 Patient and procedural characteristics

	Postoperative delirium ($n = 93$)	No postoperative delirium ($n = 582$)	All patients ($n = 675$)	Missings n (%)	p Values
Age, years: median (IQR)	82 (79–85)	81 (76–85)	81 (77–85)		0.046
Sex, male: n (%)	37 (40)	271 (47)	308 (46)		0.223
Preoperative comorbidities, conditions, and medication					
EuroSCORE	16 (12–25)	14 (10–20)	14 (10–21)	6 (1)	0.006
Frailty: n (%)	47 (51)	257 (44)	304 (45)		0.251
Hypertension: n (%)	66 (71)	359 (62)	425 (63)		0.085
Diabetes: n (%)	30 (32)	172 (30)	202 (30)		0.597
Transient ischemic attack: n (%)	12 (13)	85 (15)	97 (14)		0.664
Stroke: n (%)					0.05
No	84 (90)	508 (87)	592 (88)		
Ischemic	6 (7)	69 (12)	75 (11)		
Hemorrhagic	3 (3)	5 (1)	8 (1)		
Carotid artery stenosis: n (%)	17 (18)	35 (6)	52 (8)		<0.001
Aortic valve indexed body to surface area: median (IQR)	0.36 (0.30–0.48)	0.39 (0.32–0.47)	0.38 (0.32–0.48)		0.217
Heart failure, NYHA class 3 or 4: n (%)	55 (59)	306 (53)	361 (54)		0.239
Atrial fibrillation: n (%)	34 (37)	199 (34)	233 (35)		0.656
Estimated glomerular filtration rate (ml/min/1.73m^2) median (IQR)	58 (47–69)	59 (45–74)	59 (45–73)	1 (0.1)	0.633
Procedure specific characteristics					
Type of anesthesia, general: n (%)	34 (37)	94 (16)	128 (19)		<0.001
Duration of procedure, minutes: median (IQR)	153 (135–182)	140 (123–160)	143 (124–164)	1 (0.1)	<0.001
Approach, transfemoral: n (%)	63 (68)	511 (88)	574 (85)		<0.001
Aortic valve type, balloon expandable: n (%)	70 (75)	414 (71)	551 (73)		0.411
Intraoperative hemodynamic variables and medication					
Area under the blood pressure, mean blood pressure < 100 mmHg, mmHg min: median (IQR)	2530 (1340–4110)	2050 (1160–3080)	2310 (1190–3310)	14 (2)	0.006
Area under the blood pressure, mean blood pressure < 90 mmHg, mmHg min: median (IQR)	1260 (643–2760)	1030 (487–1960)	1110 (505–2080)	14 (2)	0.004
Area under the blood pressure, mean blood pressure < 80 mmHg, mmHg min: median (IQR)	536 (266–1620)	395 (147–964)	414 (163–1080)	14 (2)	0.001
Area under the blood pressure, mean blood pressure < 70 mmHg, mmHg min: median (IQR)	208 (69–701)	106 (26–358)	119 (31–402)	14 (2)	<0.001
Area under the blood pressure, mean blood pressure < 60 mmHg, mmHg min: median (IQR)	75 (16–233)	23 (0.25–90)	26 (3–99)	14 (2)	<0.001

of a linear slope component (slope from last available blood pressure measurement to the next available measurement).[25] Patients without any POD assessments during the hospital stay were used for the multiple imputation procedure, but were excluded after imputation and not included in the primary and sensitivity analyses.

Statistical analysis

All analyses were performed using R (release 3.5.1). Skewed continuous data were presented as medians with interquartile ranges (IQR). Categorical variables were expressed as frequencies (percentage). Based on assessment for nonlinearity, age and areas under the MBP threshold were analyzed in regression models after transformation with restricted cubic splines with three knots. The association between IOH based on five MBP thresholds and occurrence of POD was analyzed with multivariable logistic regression models using penalized maximum likelihood estimation ("lrm" function, "rms"-package, release 5.1-3.1). Bootstrapping ($n = 500$ repetitions) and penalization were used to determine and optimize model performance. Penalization is a shrinkage procedure to avoid overfitting of the model.[29] The "rms" function "pentrace" was used for the selection of penalty factors

TABLE 2 Intraoperative hypotension, area under various mean arterial blood pressure thresholds, and occurrence of postoperative delirium

	Index value/ category	Reference value/ category	Adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)	Penalized adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)
Area under the blood pressure, mean arterial blood pressure < 100 mmHg				
Area under the blood pressure, mean arterial blood pressure < 100 mmHg, mmHg min	1190	3310	0.96 (0.51–1.80)	1.08 (0.74–1.56)
Area under the blood pressure, mean arterial blood pressure < 90 mmHg				
Area under the blood pressure, mean arterial blood pressure < 90 mmHg, mmHg min	505	2080	1.00 (0.49–2.03)	1.08 (0.75–1.55)
Area under the blood pressure, mean arterial blood pressure < 80 mmHg				
Area under the blood pressure, mean arterial blood pressure < 80 mmHg, mmHg min	163	1080	1.13 (0.52–2.45)	1.08 (0.78–1.50)
Area under the blood pressure, mean arterial blood pressure < 70 mmHg				
Area under the blood pressure, mean arterial blood pressure < 70 mmHg, mmHg min	31	402	1.38 (0.63–3.03)	1.08 (0.83–1.40)
Area under the blood pressure, mean arterial blood pressure < 60 mmHg				
Area under the blood pressure, mean arterial blood pressure < 60 mmHg, mmHg min	3	99	1.65 (0.84–3.24)	1.06 (0.88–1.28)

Note: Five separate logistic regression models were fitted for five mean arterial blood pressure thresholds on the association between intraoperative hypotension and postoperative delirium. The results are expressed as a scaled adjusted odds ratio between the 75th and 25th percentile and as a scaled penalized adjusted odds ratio with 99% confidence intervals. The index value represents the 25th percentile of a continuous variable or index category of a categorical variable. The reference value represents the 75th percentile of a continuous variable or reference category of a categorical variable.

with a vector containing the following predefined penalties: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24. The results of the regression analyses were expressed as scaled adjusted odds ratios (OR) between the 75th and 25th percentile with 99% confidence intervals (CI). Statistical significance was defined as a two-sided α of 0.01.

During data analysis, a profound difference in delirium incidence and areas under various MBP thresholds was noted. Therefore, post hoc secondary analyses were performed to compare the association between profound IOH, indicated by MBP < 70 mmHg and < 60 mmHg, and occurrence of POD in patients who underwent procedural sedation or general anesthesia. In response to peer review, we added additional sensitivity analyses for patients with carotid artery stenosis, frail patients, and a non-transfemoral approach. Due to the limited numbers of patients in all subgroups for the post hoc sensitivity analyses, the numbers of potential confounders included in these models were limited compared with the primary analyses. Age (included in EuroSCORE), sex (included in EuroSCORE, and frailty (comparable incidence in both groups) were not included in the sensitivity analyses.

RESULTS

We included 753 patients, of whom 78 (10%) were excluded because the primary outcome was missing. Of the remaining 675 patients, 93 patients (14%) developed POD. Patients who developed POD after TAVR were more often male and had a higher EuroSCORE, a smaller aortic valve area, and more frequently carotid stenosis. General anesthesia and a non-transfemoral approach were also more common among patients with POD compared with patients who did not develop POD (Table 1). Depending on the threshold, 674 (100% with MBP < 100 mmHg) and 518 patients (77% with MBP < 60 mmHg) had at least 1 min of IOH. Patients with POD had higher AUTs based on all five thresholds compared with patients who did not develop delirium (Table 1).

We did not find a statistically significant association between IOH for any threshold and occurrence of POD after TAVR. The scaled penalized adjusted ORs between the 75th and 25th percentiles for each AUT threshold varied between OR 1.08 (99% Confidence Interval (CI) 0.74–1.56) for the AUT based on MBP < 100 mmHg and OR 1.06 (99% CI 0.88–1.28) for the AUT based on MBP < 60 mmHg (Table 2, Figures 1 and 2).

The total AUTs for each defined threshold and duration of the procedure were higher in patients who underwent general anesthesia compared with patients who underwent procedural sedation (Table S1). In other words, the total area under the threshold (consisting of depth and duration) for each MBP threshold was larger for patients who underwent general anesthesia compared with procedural sedation. In addition to the main analyses that were adjusted for type of anesthesia, we performed post hoc sensitivity analyses in patients who

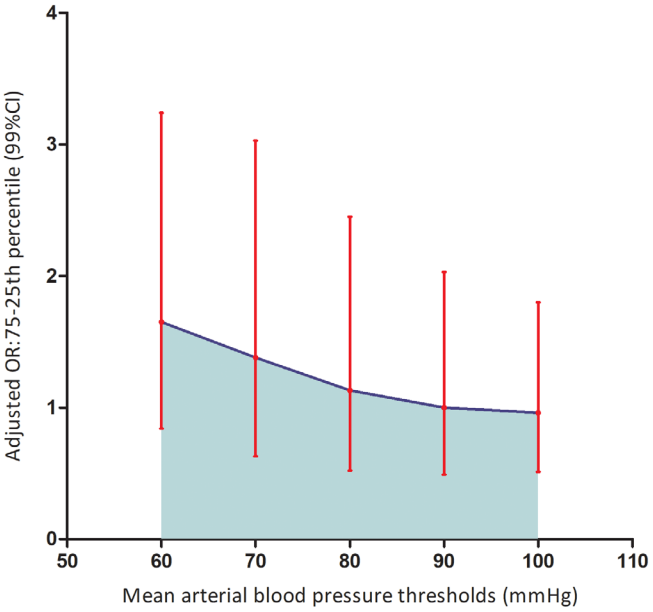

FIGURE 1 Association between mean arterial blood pressure thresholds and postoperative delirium expressed as an adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)

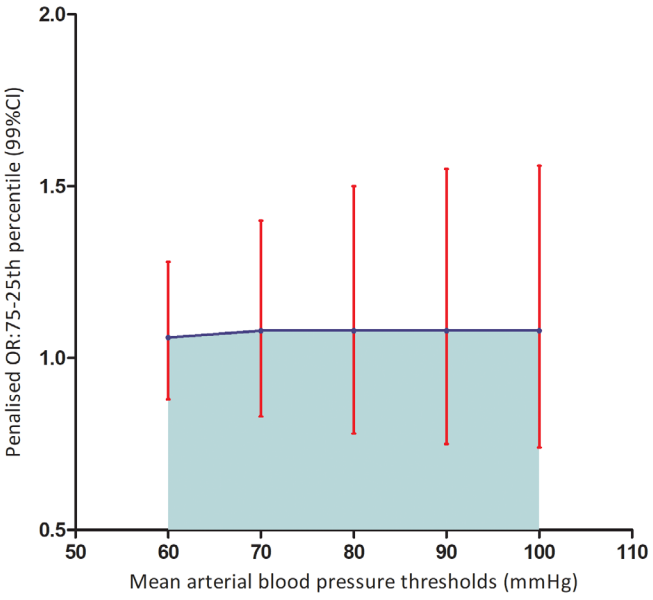

FIGURE 2 Association between mean arterial blood pressure thresholds and postoperative delirium expressed as a penalized adjusted scaled odds ratio between the 75th and 25th percentile (99% CI) [Color figure can be viewed at wileyonlinelibrary.com]

underwent general anesthesia ($n = 128$), and procedural sedation ($n = 574$). We did not find an association between MBP < 70 mmHg (general anesthesia: scaled penalized OR 1.07 (99% CI 0.65–1.75), sedation: scaled penalized OR 0.99 (99% CI 0.79–1.25)) or MBP < 60 mmHg (general anesthesia: scaled penalized OR 1.41 (99% CI 0.37–5.30), procedural sedation: scaled penalized OR 1.27 (99% CI 0.62–2.58)) and occurrence of POD after TAVR (Table S2). Nor did we find an association between other post hoc sensitivity analyses for patients with carotid artery stenosis (MBP < 70 mmHg: scaled penalized OR 1.88 (99% CI 0.87–4.06), MBP < 60 mmHg: scaled penalized OR 1.87 (99% CI 0.92–3.77)), frail patients (MBP < 70 mmHg: scaled penalized OR 1.02 (99% CI 0.77–1.35), MBP < 60 mmHg: scaled penalized OR 1.02 (99% CI 0.78–1.33)) or non-transfemoral approach (MBP < 70 mmHg: scaled penalized OR 1.11 (99% CI 0.71–1.72), MBP < 60 mmHg: scaled penalized OR 2.10 (99% CI 0.80–5.51)) (Table S2).

DISCUSSION

In summary, IOH was common during TAVR, and patients who developed POD had higher AUTs based on all predefined five MBP thresholds. Patients with POD compared with patients without POD after TAVR had a higher operative risk, smaller aortic valve area, suffered more from carotid stenosis, and underwent frequently non-transfemoral TAVR with general anesthesia. In the multivariable analyses, IOH was however not associated with POD after TAVR when adjusted for possible confounding factors, as the observed effects were clinically irrelevant. Neither was IOH associated with POD according to the type of anesthesia: the effects were small with limited clinical relevance, but with very large uncertainties in their estimates.

Due to the lack of widely accepted uniform definition of IOH, and different settings and outcome, it is difficult to define a common 'cutoff' for IOH associated adverse postoperative outcomes.[30,31] In the 2012 ACCF/AATS/SCAI/STS expert consensus document on TAVR, maintenance of an MBP of >75 mmHg (or systolic blood pressure of at least 120 mmHg) during TAVR has been advised.[32] In the current study, we analyzed data according to the five frequently used hypotension definitions pending a widely accepted definition of IOH.[30,33]

Our findings that IOH was not associated with POD may be explained by adaptation in older adults with severe aortic valve stenosis to chronic reduced cardiac output and chronic cerebral hypoperfusion.[34] Recent studies show an immediate increase in cardiac output and cerebral blood flow following TAVR, suggesting a reserved or even decreased cerebral blood flow pre-TAVR.[7,35] Our findings put forward the hypothesis that a chronic cerebral hypoperfusion pre-TAVR may result into tolerance to an acute drop in IOH with a short duration during TAVR, a phenomenon called brain ischemic preconditioning.[36–38] Another factor that may explain our findings is the so-called physiologic cerebral autoregulation, which alleviates a possible neurocognitive harmful effect of IOH.[39,40] Future prospective studies are needed to investigate the abovementioned hypothesis following TAVR.

A strength of this study is that we used continuous variables during TAVR in order to reduce loss of information, and analyzed them with restricted cubic splines. Another strength is that a multiple imputation method was used for missing data. Furthermore, In order to minimize overfitting and optimize model performance, penalization and bootstrapping methods were used.[29]

There are however several important limitations of this study. First, this is an analysis of retrospectively collected data with inherent limitations. Therefore, our results should be interpreted as hypothesis generating. Second, in the majority of cases delirium was diagnosed using DOS scores combined with clinical features. According to the local protocol, DOS scores should be registered during every shift. However, in some patients, DOS scores were not reported and/or were missing. Moreover, by using DOS scores, the hypoactive type of delirium may be easily overlooked. Third, we have excluded patients without POD assessment, which could have led to an under- or overestimation of the number of delirium cases in this study. Fourth, there may have also been other time-dependent, which could influence the incidence of delirium that we did not include in our analyses, such as blood pressure variability during rapid ventricular pacing. To facilitate precise prosthesis positioning and to reduce the risk of device embolization and malpositioning, rapid ventricular pacing is required during valve deployment for temporary reduction in cardiac output, transvalvular flow, and cardiac motion.[41] Rapid ventricular pacing was found to be associated with transient IOH, cerebral perfusion disturbances, and POD after TAVR.[19–22,42–44] Finally, our post hoc sensitivity analysis was underpowered due to the small sample size of patients undergoing TAVR with general anesthesia. Therefore, larger studies are needed to assess the effect of general anesthesia on delirium occurrence after TAVR.

In conclusion, this study shows that IOH is frequent during TAVR. Our findings do not suggest an association between IOH during TAVR and delirium thereafter. Other potential factors rather than intraoperative hypotension may explain the development of delirium among older adults undergoing this treatment.

CONFLICT OF INTEREST

None of the authors have a conflict of interest regarding the data or subject matter reported in this study.

AUTHOR CONTRIBUTIONS

Masieh Abawi: study concept and design, data collection, preparation of the manuscript, revision of the manuscript. Esther M. Wesselink: data analysis, interpretation of data, preparation of the manuscript, revision of the manuscript. Nynke H. M. Kooistra: data collection, study concept and design, revision of the manuscript. Teus H. Kappen: data analysis, interpretation of data. Pierfrancesco Agostoni: revision of the manuscript. Marielle Emmelot-Vonk: revision of the manuscript. Wietze Pasma: data collection, interpretation of data, revision of the manuscript. Charlotte S. van Dongen: data collection, revision of the manuscript. Romy C. van Jaarsveld: data collection, revision of the manuscript. Wilton A. van Klei: interpretation of data, revision of the manuscript. Pieter A. F. M. Doevendans: revision of the manuscript. Arjen J. C. Slooter: revision of the manuscript. Pieter R. Stella: revision of the manuscript, principle investigator of this study.

SPONSOR'S ROLE

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1: Patient and procedure characteristics.

Table S2: Association between area under the mean arterial blood pressure thresholds and occurrence of postoperative delirium.

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