



Original Contribution



Differences in incidence of post-induction hypotension depending on the time of day: a post-hoc propensity score matched analysis

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HIGHLIGHTS

- Susceptibility to anaesthesia induced physiological changes may differ by time of day.
- Post-induction hypotension incidence is higher in the morning compared to the afternoon in propensity score matched analysis.
- No difference in instantaneous baroreflex sensitivity was found between the morning and afternoon groups

ARTICLE INFO

Keywords:

Circadian rhythm

Diurnal

Haemodynamics

Hypotension

Induction

Propensity score matching

ABSTRACT

Background: Many physiological processes show a diurnal rhythm, including sympathetic and parasympathetic tone, adrenal hormone secretion and blood pressure. Since these physiological rhythms may affect the sensitivity to anaesthesia, we hypothesised that the time of day when anaesthesia induction occurs may affect the incidence of post-induction hypotension.

Methods: This was a post-hoc propensity score matched analysis of prospectively collected blood pressure data of 760 elective non-cardiac surgery patients receiving general anaesthesia. The primary endpoint was the incidence of post-induction hypotension, defined as mean arterial pressure < 65 mmHg for at least one minute. Secondary endpoints were a > 30 % decrease in mean arterial pressure, and baroreflex sensitivity.

Results: In the analysis of 237 propensity score matched pairs, post-induction hypotension was more frequent if anaesthesia induction occurred in the morning (08:00 AM - 12:00 PM) (odds ratio (OR) 1.48, 95 % confidence interval (CI): 1.00–2.20, $p = 0.049$). Secondary analyses of the matched cohort showed that a > 30 % decrease in mean arterial pressure was likewise more frequent in the morning than the afternoon (12:00 PM – 17:00 PM) (OR 1.45, 95 % CI: 1.00–2.11, $p = 0.0499$), but no differences in instantaneous baroreflex sensitivity were observed.

Conclusions: Post-induction hypotension was more frequent in the morning compared to the afternoon. While this finding is in line with the presumed physiological mechanisms, it may be affected by unmeasured confounding.

Abbreviations: ASMD, Absolute standardized mean difference; AVP, Arginine vasopressin; BP, Blood pressure; CI, Confidence interval; HPA, Hypothalamic pituitary axis; IBI, Interbeat interval; MAP, Mean arterial pressure; PIH, Post induction hypotension; PSM, Propensity score matching; OMON, Overview of medical research in the Netherlands; OR, Odds ratio; SAP, Systolic arterial pressure; SD, Standard deviation.

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<https://doi.org/10.1016/j.jclinane.2025.111984>

Received 2 February 2025; Received in revised form 2 July 2025; Accepted 21 August 2025

Available online 3 September 2025

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These findings should be replicated in larger, preferably randomised, studies to confirm whether a causal relationship between the time of day of anaesthesia induction and post-induction hypotension exists.

Clinical registration number

This study was registered in the Dutch Medical Research in Humans (OMON) register on 18 June 2019 (ID: NL7810). The study was approved by the Medical Ethics Committee of the Amsterdam UMC, location AMC, Netherlands in December 2018 (NL 6748.018.18; 2018).

1. Introduction

Catecholamine levels, glucocorticoid levels, vagal tone, and blood pressure (BP) vary throughout the day [1,2], following a circadian or diurnal pattern regulated by the ‘master clock’ in the suprachiasmatic nuclei of the hypothalamus [3]. For example, vagal activity peaks in the morning and has a trough in the evening [2]. The importance of circadian rhythms in the cardiovascular and endocrine systems has been recognised [4,5], and knowledge of the effect of anaesthesia on the circadian clock is increasing [6]. Conversely, the disturbance of the physiological diurnal pattern in BP is a known risk factor of post-induction hypotension (PIH) [7], and these diurnal changes, especially in vagal tone, may alter the physiological capacity to react to the haemodynamic stress induced by anaesthesia.

One of the major mechanisms causing PIH during general anaesthesia is the sympatholytic activity of the drugs administered, especially propofol, which decreases both baseline sympathetic nervous system activity and the baroreflex response to a decrease in arterial pressure [8–10]. Vagal tone, on the other hand, is reduced to a lesser extent during anaesthesia [10,11], and is even stimulated to some degree by opioid administration [12]. We hypothesise that the sympatholytic action of anaesthesia, with relatively little simultaneous parasympatholytic action, at the time of the diurnal peak in vagal tone [2] may lead to a relatively higher vagal tone during induction of anaesthesia in the morning compared to the afternoon. In turn, this relative imbalance in autonomous activity would result in a higher incidence of PIH in the morning compared to the afternoon. If patients receiving anaesthesia in the morning have a higher risk of PIH, clinicians may use this knowledge to adjust their induction strategy, e.g. by initiating pre-emptive vasopressor treatment.

2. Methods

2.1. Study design

This post-hoc propensity score matched analysis included prospectively collected data of the single centre observational ‘Prediction of Post-Induction Hypotension with Arterial Pulse wave applied Machine Learning’- study (OMON, ID: NL7810). This study was approved under the Medical Research involving Human Subjects Act by the Amsterdam UMC institutional review board in December 2018 (NL 67484.018.18). Data were collected from January 2019 until July 2023. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. Reporting was done in accordance with the STROBE statement [13].

2.2. Study participants

Adult patients (≥ 18 years) undergoing general anaesthesia for elective non-cardiac surgery were eligible for inclusion. Exclusion criteria were inability to measure continuous non-invasive BP with a finger cuff, structural cardiac pathology of the right ventricle, abnormal anatomy of the fingers and cardiac arrhythmias with high heart rate (>100 beats per minute). All participants provided informed consent prior to study measurements.

2.3. Objectives

The primary aim was to evaluate whether the incidence of PIH differs between general anaesthesia initiated in the morning (before 12:00 PM) compared to anaesthesia initiated in the afternoon (after 12:00 PM). PIH was defined as a MAP <65 mmHg for one minute, in the twenty minutes after the start of induction of general anaesthesia, or until surgical incision if this occurred earlier. Secondary aims were:

1. To evaluate whether the incidence of a > 30 % decrease in MAP compared to MAP at the pre-operative holding complex for at least one minute differs between patients receiving general anaesthesia in the morning compared to the afternoon. MAP <65 mmHg for one minute was chosen as primary outcome over >30 % decrease in MAP both due to MAP <65 mmHg being used as the threshold for hypotension in our institution, and uncertainty about the optimal baseline for relative thresholds for hypotension [14].
2. To evaluate whether the nadir MAP after induction differs between patients receiving anaesthesia in the morning compared to the afternoon.
3. To evaluate whether baroreflex sensitivity – a measure of autonomous nervous system activity – differs pre-operatively between patients in the morning compared to the afternoon. Instantaneous baroreflex sensitivity is expressed in gain and tau, i.e. delay, and calculated using the cross-correlation method outlined by Westerhof et al. [15] In short, interbeat intervals (IBI) were derived from arterial blood pressure waveforms, sampled at 200 Hz. Systolic arterial pressure (SAP) was extracted from the same continuous arterial pressure waveforms. To reduce the impact of irregular timing between IBI and align the data on a uniform time axis, the data were resampled to 1 Hz using a cubic spline interpolation technique. Baroreflex sensitivity was determined by calculating the correlation between IBI and SAP over a 10 s sliding window. For each window, the correlation between the two signals is calculated six times, as the time delay between IBI and SAP is increased, from 0 to 5 s. The time delay with the highest positive correlation coefficient is selected, with the slope of the corresponding regression line representing the baroreflex gain, while the time delay represents the baroreflex tau.

2.4. Data collection

Beat-to-beat BP data were collected in addition to BP data averaged over 20-s intervals using the ClearSight system (Edwards Lifesciences LTD, Irvine, CA, USA) from the pre-operative holding area to surgical incision. Only standard of care blood pressure monitoring, either intermittent sphygmomanometry using an upper arm cuff or an arterial line, was available to clinicians. Researchers were present in the operating theatre to record all haemodynamically relevant events, such as type, dose, and speed of administration of vasoactive medication, for the duration of anaesthesia induction, and did not intervene in anaesthetic or haemodynamic management. Patient characteristics were obtained from the electronic medical record. Pre-emptive vasopressor therapy was defined as any vasopressor initiated before the administration of the first anaesthetic agent, or within the first minute thereafter.

Prior to analysis, beat-to-beat data were first evaluated for the presence of artefacts, e.g. due to ipsilateral sphygmomanometry or patient repositioning. The presence of PIH was evaluated using the 20-s

averaged BP data, both with and without data restrictions to determine possible false-positive labelling of hypotension. If a discrepant labelling of PIH between the methods was found, two researchers (JTMT, WHV) individually checked the BP data for PIH. Only if both researchers found that data restrictions had led to a false-negative label of PIH, the label was changed. Baseline MAP was defined as the average of 5 min of BP data collected in the pre-operative holding area. The lowest MAP value for each patient was defined as the 5th percentile of all MAP values after induction, excluding poor signal quality and outliers. A detailed description of all data analyses is available in an earlier work on these study data [16].

2.5. Sample size calculation

A sample size of 750 non-cardiac surgery patients was originally determined for the study objective of the 'Prediction of Post-Induction Hypotension' study. This sample size could not be altered due to the post-hoc nature of the present study. To estimate the adequacy of the sample size, confidence intervals are provided for all effect estimates.

2.6. Statistical analysis

Descriptive statistics of normally distributed continuous data were presented as mean with standard deviation (SD), or as median [25th percentile, 75th percentile] when not normally distributed. Categorical data were presented as frequencies with percentages.

Missing values of baseline MAP were assumed to be missing at random and imputed using the *mice* package for R (R Foundation for Statistical Computing, Vienna, Austria), based on all available pre-operative patient characteristics [17]. We used random forest imputation to impute five datasets, using 10 iterations for each imputation, and examined the distribution of the observed and imputed values using both density- and strip plots [18].

Propensity score matching (PSM) was performed using the *MatchIt* package for R (R foundation for statistical computing, Vienna, Austria) [19] to account for the non-randomized nature of surgical planning when estimating the effect of anaesthesia in the afternoon versus the morning. The cutoff for morning versus afternoon anaesthesia inductions was pragmatically placed at 12:00 PM, the approximate halfway point of an elective surgery program in our institution. No study measurements were performed in the evening or night.

The variables used to determine the propensity scores were identified in published literature [20–24], including patient demographics, medical history and home medication use, and were supplemented by factors used in local protocols to determine surgery planning, such as surgery type and the presence of diabetes mellitus. Matching was performed using the 'nearest neighbour method', using a calliper width of 0.2 SD of the logit of the propensity score, in a 1 to 1 matching ratio [25]. Balance of matching variables and non-matched anaesthesia related variables, i.e., anaesthetic or vasopressor drug use and doses, was assessed using the absolute standardised mean difference (ASMD) and the empirical cumulative distribution functions [26]. Balance was deemed acceptable when the ASMD was less than 10 % for all matched variables. Non-matched variables with an ASMD > 10 % were entered into the logistic regression analysis as covariates to correct for residual confounding when a relation to the outcome, i.e. PIH, was clinically plausible or likely.

Logistic regression analysis was applied to assess the association between the timing of anaesthesia induction and PIH defined as a MAP < 65 mmHg for one minute, and between timing of anaesthesia and a > 30 % decrease in MAP compared to baseline for one minute, in both the unmatched and the matched cohort, accounting for the paired nature of the data after matching [27]. Effect estimates were reported as odds ratio (OR) with 95 % confidence intervals (CI). The *E*-value, a measure to define the minimum required strength of an unmeasured confounder to nullify the observed effect size, was calculated for the analyses on

MAP < 65 mmHg and > 30 % MAP decrease [28].

Secondary analyses on the association between timing of anaesthesia and baroreflex gain and time delay (τ) were performed using linear regression analysis on both the matched and unmatched cohorts. Baroreflex gain values were log-transformed prior to analysis. Patients with a pacemaker and/or known history of (paroxysmal) atrial fibrillation were excluded from the baroreflex sensitivity analyses due to the expected irregular ventricular response to BP variation [29]. Nadir MAP in the morning and afternoon was compared using a paired *t*-test.

All analyses were performed using R version 4.3.2.

3. Results

Of the 760 study measurements performed, 720 were suited for analysis. (Fig. 1) PSM resulted in 237 pairs, or 474 patients in total. (Fig. 1 & Table 1) On average, the likelihood of being in the morning group versus being in the afternoon group differed by 4.6 % across the matched pairs. ASMD for all matched variables was substantially reduced to below 10 % (Fig. 2 and Table 1) after PSM. Characteristics of anaesthesia induction, including vasopressor use, norepinephrine dose, opioid choice, and propofol induction dose, were well-balanced between the morning and afternoon (Table 2). The distribution of the propensity scores and distribution of variables before and after matching are presented in Supplementary Figs. 1 and 2. Baseline MAP was imputed in 27 (5.7 %) patients. Continuous intra-arterial BP monitoring was initiated before induction in 17 (7.2 %) patients in the morning, compared to 14 (6.3 %) in the afternoon.

3.1. Primary objective

Before matching, PIH occurred in 174 (36.4 %) patients undergoing anaesthesia in the morning, compared to 64 (26.4 %) in the afternoon. In the matched cohort, PIH occurred in 84 (35.4 %) of patients in the morning group, compared to 64 (27.0 %) in the afternoon group. Unadjusted logistic regression in the unmatched cohort showed that anaesthesia induction in the morning was associated with an increased incidence of PIH (OR 1.59, 95 % CI: 1.14–2.25, $p = 0.008$). Logistic regression analysis after matching showed that general anaesthesia initiated in the morning was associated with an increased incidence of PIH (OR 1.48, 95 % CI: 1.00–2.20, $p = 0.049$). The *E*-value for the point estimate was 1.73, and 1.02 for the confidence interval.

3.2. Secondary objectives

In the unmatched cohort, 201 (42.1 %) patients receiving anaesthesia in the morning experienced a > 30 % decrease in MAP, compared to 86 (35.6 %) in the afternoon. After matching, a > 30 % decrease in MAP compared to baseline occurred in 104 (43.9 %) patients in the

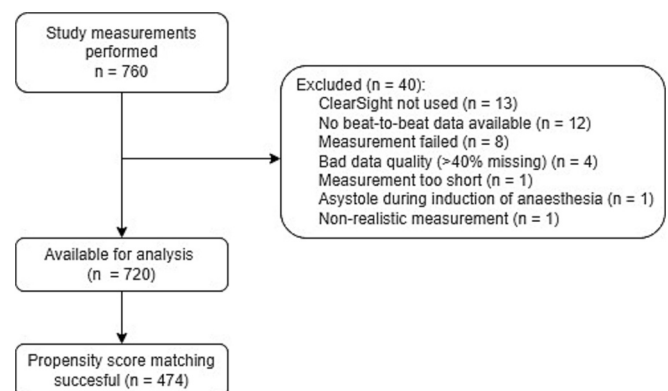


Fig. 1. Patient in and exclusion, and number of patients in the propensity score matched cohort.

Table 1

Description of variable distribution of patients undergoing anaesthesia induction before and after matching. Values are mean (SD), number (proportion), or proportion.

	Before matching				After matching			
	Morning (n = 478)	Afternoon (n = 242)	Std. Mean Diff.	eCDF Max	Morning (n = 237)	Afternoon (n = 237)	Std. Mean Diff.	eCDF Max
Distance	0.31	0.40	64.7 %	0.31	0.38	0.39	4.6 %	0.05
Demographics								
Age	55.4 (16.4)	55.2 (16.2)	-1.0 %	0.04	54.7 (16.3)	55.0 (16.3)	2.2 %	0.06
Female sex	239 (50.0 %)	124 (51.2 %)	2.5 %	0.01	121 (51.1 %)	122 (51.5 %)	0.8 %	0.00
Body Surface Area	1.96 (0.23)	1.97 (0.24)	6.8 %	0.06	1.97 (0.24)	1.97 (0.23)	-0.2 %	0.06
Body Mass Index								
<18.5 kg m ⁻²	8 (1.7 %)	2 (0.8 %)	-9.4 %	0.01	2 (0.8 %)	2 (0.8 %)	0.0 %	0.00
18.5–25.0 kg m ⁻²	206 (43.1 %)	117 (48.3 %)	10.5 %	0.05	111 (46.8 %)	114 (48.1 %)	2.5 %	0.01
>25.0 kg m ⁻²	264 (55.2 %)	123 (50.8 %)	-8.8 %	0.04	124 (52.3 %)	121 (51.1 %)	-2.5 %	0.01
ASA physical status classification								
I	108 (22.6 %)	34 (14.0 %)	-24.6 %	0.09	32 (13.5 %)	34 (14.3 %)	2.4 %	0.01
II	248 (51.9 %)	117 (48.3 %)	-7.1 %	0.04	120 (50.6 %)	116 (48.9 %)	-3.4 %	0.02
III	119 (24.9 %)	87 (36.0 %)	23.0 %	0.11	82 (34.6 %)	83 (35.0 %)	0.9 %	0.00
IV	3 (0.6 %)	4 (1.7 %)	8.0 %	0.01	3 (1.3 %)	4 (1.7 %)	3.3 %	0.00
Surgery type								
Orthopaedic	85 (17.8 %)	42 (17.4 %)	-1.1 %	0.00	39 (16.5 %)	41 (17.3 %)	2.2 %	0.01
Gynaecology	70 (14.6 %)	42 (17.4 %)	7.2 %	0.03	44 (18.6 %)	41 (17.3 %)	-3.3 %	0.01
Urology	69 (14.4 %)	26 (10.7 %)	-11.9 %	0.04	26 (11.0 %)	26 (11.0 %)	0.0 %	0.00
Vascular	62 (13.0 %)	40 (16.5 %)	9.6 %	0.04	34 (14.3 %)	39 (16.5 %)	5.7 %	0.02
Lower GI	56 (11.7 %)	25 (10.3 %)	-4.6 %	0.01	25 (10.5 %)	24 (10.1 %)	-1.4 %	0.00
Upper GI	44 (9.2 %)	10 (4.1 %)	-25.5 %	0.05	6 (2.5 %)	10 (4.2 %)	8.5 %	0.02
Neurosurgery	21 (4.4 %)	13 (5.4 %)	4.3 %	0.01	15 (6.3 %)	13 (5.5 %)	-3.7 %	0.01
Otorhinolaryngology	26 (5.4 %)	16 (6.6 %)	4.7 %	0.01	19 (8.0 %)	16 (6.8 %)	-5.1 %	0.01
Ophthalmology	7 (1.5 %)	3 (1.2 %)	-2.0 %	0.00	3 (1.3 %)	3 (1.3 %)	0.0 %	0.00
Endovascular	6 (1.3 %)	5 (2.1 %)	5.7 %	0.01	5 (2.1 %)	5 (2.1 %)	0.0 %	0.00
Maxillofacial	6 (1.3 %)	2 (0.8 %)	-4.7 %	0.00	3 (1.3 %)	2 (0.8 %)	-4.7 %	0.00
Reconstructive/plastic	4 (0.8 %)	3 (1.2 %)	3.6 %	0.00	2 (0.8 %)	2 (0.8 %)	0.0 %	0.00
Other	22 (4.6 %)	15 (6.2 %)	6.6 %	0.02	16 (6.8 %)	15 (6.3 %)	-1.7 %	0.00
Cardiac surgical risk[†]								
Low	144 (30.1 %)	71 (29.3 %)	-1.7 %	0.01	74 (31.2 %)	70 (29.5 %)	-3.7 %	0.02
Average	279 (58.4 %)	153 (63.2 %)	10.1 %	0.05	149 (62.9 %)	149 (62.9 %)	0.0 %	0.00
High	55 (11.5 %)	18 (7.4 %)	-15.5 %	0.04	14 (5.9 %)	18 (7.6 %)	6.4 %	0.02
Medical history								
Arterial Hypertension	150 (31.4 %)	90 (37.2 %)	12.0 %	0.06	79 (33.3 %)	86 (36.3 %)	6.1 %	0.03
History of Oncological Disease	122 (25.5 %)	50 (20.7 %)	12.0 %	0.05	55 (23.2 %)	50 (21.1 %)	5.2 %	0.02
History of Neurological Disease	75 (15.7 %)	47 (19.4 %)	-9.4 %	0.04	46 (19.4 %)	47 (19.8 %)	-1.1 %	0.00
Diabetes Mellitus type II	40 (8.4 %)	31 (12.8 %)	13.3 %	0.04	27 (11.4 %)	28 (11.8 %)	1.3 %	0.00
Chronic Kidney Injury	37 (7.7 %)	47 (19.4 %)	29.5 %	0.12	35 (14.8 %)	44 (18.6 %)	9.6 %	0.04
Peripheral Artery Disease	18 (3.8 %)	12 (5.0 %)	5.5 %	0.01	10 (4.2 %)	12 (5.1 %)	3.9 %	0.01
Chronic Obstructive Pulmonary Disease (any severity)	17 (3.6 %)	16 (6.6 %)	12.3 %	0.03	13 (5.5 %)	15 (6.3 %)	3.4 %	0.01
Diabetes Mellitus type I	10 (2.1 %)	1 (0.4 %)	-26.2 %	0.02	2 (0.8 %)	1 (0.4 %)	-6.6 %	0.00
Heart failure (any NYHA)	10 (2.1 %)	3 (1.2 %)	-7.7 %	0.01	1 (0.4 %)	3 (1.3 %)	7.6 %	0.01
History of Kidney Transplantation	7 (1.5 %)	8 (3.3 %)	10.3 %	0.02	5 (2.1 %)	8 (3.4 %)	7.1 %	0.01
Smoking status								
Current smoker	62 (13.0 %)	34 (14.0 %)	3.1 %	0.01	34 (14.3 %)	33 (13.9 %)	-1.2 %	0.00
Never smoked	208 (43.5 %)	109 (45.0 %)	3.1 %	0.02	109 (46.0 %)	108 (45.6 %)	-0.8 %	0.00
Unknown	66 (13.8 %)	34 (14.0 %)	0.7 %	0.00	39 (16.5 %)	33 (13.9 %)	-7.3 %	0.03
Previous smoker	142 (29.7 %)	65 (26.9 %)	-6.4 %	0.03	55 (23.2 %)	63 (26.6 %)	7.6 %	0.03
Medication use								
Betablocker use	80 (16.7 %)	44 (18.2 %)	3.7 %	0.01	40 (16.9 %)	43 (18.1 %)	3.3 %	0.01
Diuretic use	59 (12.3 %)	35 (14.5 %)	6.0 %	0.02	29 (12.2 %)	35 (14.8 %)	7.2 %	0.03
COX-inhibitor use	45 (9.4 %)	29 (12.0 %)	7.9 %	0.03	28 (11.8 %)	28 (11.8 %)	0.0 %	0.00

Abbreviations: ASA: American society of anaesthesiologists, BMI: body mass index, COX: cyclo-oxygenase, GI: gastro-intestinal, MAP: mean arterial pressure, NYHA: New York Heart Association.

[†] According to 2022 European Society for Cardiology guidelines.

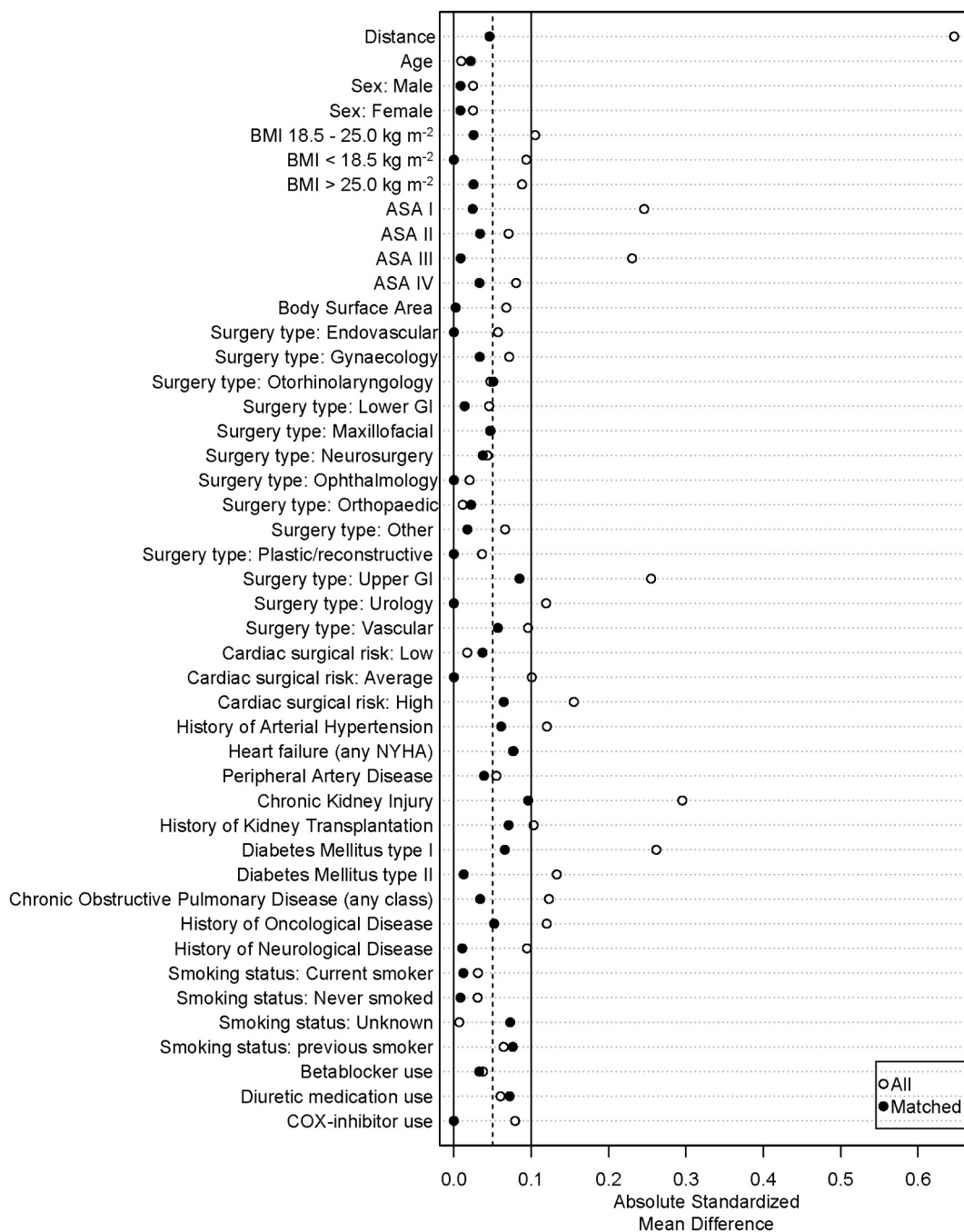


Fig. 2. LovePlot illustrating covariate balance between morning and afternoon anaesthesia induction before and after propensity score matching. All (unfilled circle) represents the unmatched cohort, Matched (filled circle) represents the propensity score matched cohort. The vertical line at 0.1 absolute standardized mean difference is a graphical representation of the threshold of acceptable balance. Abbreviations: ASA: American Society of Anaesthesiologists, BMI: body mass index, COX: cyclo-oxygenase, GI: gastrointestinal, NYHA: New York Heart Association Functional Classification.

morning, and in 83 (35.0 %) patients in the afternoon. Before matching, logistic regression analysis showed no significant difference in incidence of >30 % MAP decrease in the morning versus the afternoon (OR 1.32, 95 % CI 0.96–1.82, $p = 0.092$). After matching, anaesthesia induction in the morning was associated with higher odds of >30 % decrease in MAP compared to baseline (OR 1.45, 95 % CI: 1.00–2.11, $p = 0.0499$). The E -value for the point-estimate was 1.70, and 1.02 for the confidence interval. Nadir MAP after induction was 70.2 (14.0) mmHg in the morning compared to 73.7 (14.5) mmHg in the afternoon (estimated difference 3.5 mmHg, 95 % CI 0.9–6.2, $p = 0.009$).

Instantaneous baroreflex gain and delay could be calculated in 432

patients in the matched cohort. Median baroreflex gain was 8.4 [4.4, 14.5] mmHg·sec⁻¹ in the morning compared to 8.4 [4.7, 15.9] mmHg·sec⁻¹ in the afternoon. Linear regression analysis found no statistically significant difference between baroreflex gain in the afternoon compared to the morning ($\beta = 1.07$, 95 % CI: 0.90–1.27, $p = 0.469$). Median baroreflex tau, did not differ between patients receiving anaesthesia in the afternoon compared to the morning, either ($\beta = 0.85$, 95 % CI: 0.72–1.01, $p = 0.058$).

Table 2

Characteristics of anaesthesia induction of patients undergoing anaesthesia induction in the morning and afternoon, including distribution and balance before and after propensity score matching. Values are number (proportion), mean (SD), median [25th percentile, 75th percentile], or proportion.

	Before matching				After matching			
	Morning (n = 478)	Afternoon (n = 242)	Std. Mean Diff.	eCDF Max	Morning (n = 237)	Afternoon (n = 237)	Std. Mean Diff.	eCDF Max
MAP at baseline [†]	96.4 (13.8)	98.4 (14.6)	13.8 %	0.07	98.2 (14.0)	98.2 (14.3)	0.2 %	0.05
Remifentanyl use	122 (25.5 %)	62 (25.6 %)	0.2 %	0.00	68 (28.7 %)	62 (26.2 %)	-5.8 %	0.03
Sufentanil use	377 (78.9 %)	191 (78.9 %)	0.1 %	0.00	180 (75.9 %)	186 (78.5 %)	6.2 %	0.03
Propofol bolus given	393 (82.2 %)	201 (83.1 %)	2.2 %	0.01	195 (82.3 %)	197 (83.1 %)	2.2 %	0.01
Propofol TCI use	87 (18.2 %)	39 (16.1 %)	-5.7 %	0.02	41 (17.3 %)	39 (16.5 %)	-2.3 %	0.01
Rocuronium use	357 (74.7 %)	180 (74.4 %)	-0.7 %	0.00	170 (71.7 %)	176 (74.3 %)	5.8 %	0.03
Pre-emptive vasopressor administration [‡]	149 (31.2 %)	89 (36.8 %)	11.6 %	0.06	79 (33.3 %)	87 (36.7 %)	7.0 %	0.03
Propofol induction dose (mg kg ⁻¹)	2.1 (0.8)	2.0 (0.9)	-6.0 %	0.08	2.1 (0.8)	2.1 (0.8)	-1.3 %	0.06
Total noradrenalin dose during induction (µg)	25.0 [0.0, 46.1]	29.2 [0.2, 50.6]	12.3 %	0.10	25.8 [0.0, 46.9]	29.0 [0.0, 50.7]	7.0 %	0.08

Abbreviations: eCDF: empirical cumulative distribution function, MAP: mean arterial pressure, Std.: Standardised, TCI: Target Controlled Infusion.

[†] Baseline was defined as MAP in the pre-operative holding area.

[‡] Pre-emptive vasopressor: any vasopressor use before anaesthesia induction, or during the first minute thereafter.

4. Discussion

In summary, our matched analysis suggests that PIH occurs more frequently in patients undergoing general anaesthesia induction in the morning compared to the afternoon. Similarly, more patients experience a > 30 % decrease in MAP compared to baseline in the morning compared to the afternoon, and nadir MAP was lower in the morning compared to the afternoon. The secondary analyses performed to compare baroreflex sensitivity in the morning and the afternoon found no statistically significant differences in baroreflex gain or tau in the matched cohort.

The higher incidence of PIH and lower nadir MAP in the morning compared to the afternoon after matching are in line with our hypothesis. Surgical planning is determined by various patient, specialty, and logistical factors, and the time of day when surgery is planned may be connected indirectly to factors influencing PIH. The observed balance across all patient and anaesthesia related factors was excellent after PSM, reducing the likelihood that residual imbalance in these variables affected our results. For example, variables such as the use of pre-emptive vasopressor treatment, which could not be used for propensity score calculation, was as frequent in the morning as it was in the afternoon due to the balancing effect of the other variables.

Our secondary analyses showed that baroreflex sensitivity and baroreflex time delay did not differ between the morning and the afternoon, in contrast to a previous study with a constant routine that found a clear diurnal rhythm in vagal tone [2]. Given the robust methods of this earlier work, instantaneous baroreflex sensitivity may either not be sensitive enough to detect a diurnal rhythm in vagal tone. Alternatively, our sample size may be insufficient to detect a difference in vagal tone, or the use of 12:00 PM as a cutoff value may obscure the difference observed earlier [2]. Alternatively, diurnal rhythms in other neurohormonal systems, i.e., arginine vasopressin (AVP) levels [30,31], catecholamines [2], the hypothalamic-pituitary-adrenal (HPA) axis [32], and the renin-angiotensin-aldosterone system [33], may underly the diurnal rhythm in PIH incidence.

While awareness of the relevance of circadian patterns in BP in the context of anaesthesia is growing [7,34,35], no direct comparison of the incidence of anaesthesia-induced hypotension between morning and afternoon has been performed before to our knowledge. One small trial which randomly assigned 84 patients to either morning (08:00–12:00) or evening (18:00–22:00) surgery found no difference in perioperative blood pressure in a secondary analysis [36]. However, this study may have been underpowered to detect significant differences in BP, only examined BP at five timepoints, and its interpretation is further impeded by BP generally being lower in the evening than in the afternoon [1]. A recent systematic review suggested that the body's ability to cope with

surgical stressors may be impaired in the morning compared to the afternoon [37], which may be observed in increased platelet activity in the morning [38], or the faster return of cortisol to baseline after surgery in the afternoon [39]. Finally, recovery from anaesthesia has been found to be more rapid in the afternoon than the morning, although the clinical relevance of this difference is negligible [40]. In the context of these results, the higher incidence of PIH in the morning may indicate the body's decreased ability to adjust to the stress of anaesthesia induction.

Our findings are the first to identify a diurnal difference in the incidence of PIH, although the exact physiological mechanisms remain unknown. Further research on this phenomenon is necessary, and evaluation of the underlying mechanisms might uncover novel pathways through which intraoperative haemodynamics are influenced. Potentially identifying differences at baseline – haemodynamic or otherwise - associated with an increased risk of PIH. Clinicians might use the awareness of an increased risk of PIH in the morning by adjusting their anaesthetic induction or by initiating preventative strategies, e.g. pre-emptive vasopressor treatment or fluid administration.

4.1. Limitations & strengths

There are several limitations to this study. For one, while propensity score matched analysis is a validated method of eliminating a large degree of confounding, it still holds the potential for unmeasured confounding affecting the results, especially in a single centre study. Even though we included several risk factors for PIH in our matching method, the *E*-value for both the point estimate and lower bound of the CI are relatively low, owing to the lower bound of the 95 % CI being slightly above 1.00. Even though the confounder would have to be associated with both the time of day of anaesthesia induction and with PIH, in addition to the variables already included in the PSM procedure, a relatively minor residual confounder may result in an 95 % CI overlapping 1.00, which would affect the statistical interpretation of our results.

Secondly, due to the conception of the current study after the design of the original study, no specific data on patient chronotype, diurnal BP patterns, other measures of autonomous nervous system activity, AVP secretion, the HPA axis, or catecholamines were collected, precluding further examination of these parameters in the context of PIH. Although pre-operative fasting times in this cohort were unknown, a previous study in our institution found that patients undergoing procedures in the afternoon are fasted for solids longer, and fasted for fluids shorter, than in the morning [41]. Furthermore, fluid abstinence duration was previously found not to be associated with PIH [42].

Thirdly, no patients undergoing emergency surgery were included in this study, due to which no evening or nighttime anaesthesia induction

data were available. In effect, all anaesthesia inductions occurred between 07:45 AM and 17:00 PM.

Finally, it must be noted that the reported *p*-values and 95 % CI for both the primary and secondary outcomes indicate statistically significant results, but that both measures are close to the respective thresholds of statistical significance.

The study has several strengths. The balance in patient demographics after PSM improved to acceptable levels for all matched variables, and non-matched variables, i.e. anaesthesia characteristics, potentially affecting PIH incidence were not substantially different between the morning and afternoon groups. Furthermore, of the 242 patients in the overall afternoon group, 237 could be matched to morning patients, resulting in minimal loss of statistical power.

5. Conclusion

In conclusion, in this propensity score matched cohort of patients undergoing general anaesthesia for elective non-cardiac surgery PIH was more frequent in the morning compared to the afternoon. While we hypothesise that diurnal variation in autonomous nervous system activity is the mechanism behind this finding, we found no difference in baroreflex sensitivity between the morning and afternoon. We suggest that future research on the topic collects and accounts for patient-specific measures of autonomous nervous system activity, diurnal patterns in BP and chronotype.

CRediT authorship contribution statement

Johan T.M. Tol: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arjen J.G. Meewisse:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Sijm H. Noteboom:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Data curation. **Ward H. van der Ven:** Writing – review & editing, Project administration, Investigation. **Vincent C. Kurucz:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Lotte E. Terwindt:** Writing – review & editing, Investigation. **Eline Kho:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Data curation. **Björn van der Ster:** Writing – review & editing, Validation, Supervision, Software, Resources. **Alexander P.J. Vlaar:** Writing – review & editing, Supervision, Resources, Project administration. **Dirk J. Stenvers:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Jeroen Hermans:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mark L. van Zuylen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Denise P. Veelo:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. **Jimmy Schenk:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Funding

After design of the original “Prediction of Post-Induction Hypotension” study by the investigators, Edwards Lifesciences was contacted and supported this work. Edwards Lifesciences is the study sponsor. The Amsterdam University Academic Medical Centre will remain owner of all data and rights to publication. The physician-initiated study was supported by Edwards Lifesciences by supplying devices and finger cuffs. Edwards Lifesciences was not involved in design and conduct of this study, collection, management, analysis, interpretation of the data, preparation or review of the manuscript. Edwards Lifesciences did not have to approve the manuscript; and had no decision to submit the

manuscript for publication.

Declaration of competing interest

The Department of Anaesthesiology of the Amsterdam UMC, location AMC received financial support for this project from Edwards Lifesciences. DPV reports having received consultancy fees and research grants from Philips NV. APJV reports having received grants and consulting fees from CSL Behring, InflaRx, AM Pharma, and Edwards Lifesciences paid to the institution. All other authors declare that they have no conflict of interest.

None of the investigators of the Amsterdam UMC, location AMC have any form of (in) direct ownership in the software or hardware of Edwards and/or subject of this study. Also, no rights or claims to rights exist that might lead to financial gains for any of the authors or the Amsterdam UMC, location AMC as an institution.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Institution reports financial support was provided by Edwards Lifesciences Corporation. Denise P. Veelo reports a relationship with Philips NV that includes: consulting or advisory and funding grants paid to the institution. Alexander P.J. Vlaar reports a relationship with Edwards Lifesciences Corporation that includes: consulting or advisory and funding grants paid to the institution. Alexander P.J. Vlaar reports a relationship with CSL Behring LLC that includes: consulting or advisory and funding grants paid to the institution. Alexander P.J. Vlaar reports a relationship with InflaRx NV that includes: consulting or advisory and funding grants paid to the institution. Alexander P.J. Vlaar reports a relationship with AM Pharma that includes: consulting or advisory and funding grants paid to the institution. Markus W. Hollmann reported serving as Executive Section Editor Pharmacology with Anaesthesia & Analgesia, Section Editor Anaesthesiology with the Journal of Clinical Medicine, Editor with Frontiers in Physiology. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinane.2025.111984>.

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