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A randomized controlled trial comparing methohexital and propofol for induction in patients receiving angiotensin axis blockade

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Abstract

Background: Pharmacologic angiotensin axis blockade (AAB) has been associated with profound hypotension following anesthetic induction with propofol. To combat this problem, investigators have attempted to withhold angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) preoperatively, or evaluated the effects of different induction agents in conferring greater hemodynamic stability. To date, methohexital has not been compared with the most commonly used induction agent, propofol. Hence, the primary objective was to study the hypothesis that methohexital confers a better hemodynamic profile than propofol for anesthetic induction, in patients receiving AAB. The secondary objective was to investigate the postinduction levels of serum neurohormones in an attempt to explain the mechanisms involved.

Methods: Forty-five adult, hypertensive patients taking ACEi or ARB and scheduled for elective, noncardiac surgery completed the study. Patients were randomized to receive equi-anesthetic doses of either propofol or methohexital for anesthetic induction. Hemodynamic variables were measured and blood samples were drawn before induction and for 15 minutes afterwards.

Results: Methohexital resulted in less hypotension compared with propofol ($P = .01$), although the degree of refractory hypotension was similar ($P = .37$). The postinduction systolic blood pressure ($P = .03$), diastolic blood pressure ($P < .001$) and heart rate ($P = .03$) were significantly higher in the methohexital group. A nonsignificant elevation of serum norepinephrine and epinephrine levels was observed in the methohexital group, while serum arginine vasopressin and angiotensin II levels did not differ between groups.

Conclusion: While methohexital was shown to confer greater hemodynamic stability in patients taking ACEi/ARB, the measured hormone levels could not explain the mechanism for this effect.

Abbreviations: AAB = angiotensin axis blockade, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASA = American Society of Anesthesiologists, BMI = body mass index, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure.

Keywords: anesthetic induction, angiotensin axis blockade, baroreceptor reflex

1. Introduction

Induction of anesthesia in patients treated preoperatively with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) is often associated with significant hypotension.[1,2] One stated reason for this hypotension is the fact that pharmacologic angiotensin axis blockade may reset baroreceptor function, inhibiting compensatory heart rate (HR) increases in the face of hypotension. Up to one-third of patients

older than 45 years and presenting for surgery are now taking an ACEi or ARB,[3] and the debate regarding the appropriateness of their continuation immediately before surgery remains active and controversial.[4,5]

The intravenous induction agents methohexital and propofol have opposing effects on baroreceptor function[6]; methohexital increases baroreceptor sensitivity with a resultant increase in HR[7] while propofol decreases baroreceptor sensitivity in the face of induced hypotension.[8] Consistent with this, when induction of anesthesia in American Society of Anesthesiologists (ASA) class I and II patients were compared, methohexital was associated with better maintenance of HR and blood pressure than propofol induction.[9] Given the significant hypotension often encountered with the use of propofol for induction in patients on ACEi/ARB therapy[10] and the fact that there are now increasing concerns around the use of the more cardiostable induction agent etomidate,[11] there is a need to establish the utility of alternative cardiostable induction agents for use in the increasing number of patients presenting for surgery on ACEi/ARB therapy.

Thus, rather than investigating outcomes related to the continuation of ACEi/ARB before elective surgery,[4] this study investigated the hemodynamic feasibility of an alternative induction agent, methohexital, in this unique patient population. In addition, we wished to determine whether methohexital had different effects on circulating serum neurohormones relevant to hemodynamic homeostasis (namely arginine vasopressin, angiotensin II, norepinephrine, and epinephrine) when compared with propofol for anesthetic induction.

2. Methods

Ethical approval for this study (Protocol #3830) was provided by the Penn State Hershey Medical Center Institutional Review Board of Pennsylvania, USA on February 19, 2016. Written informed consent was obtained from all subjects. The trial was registered on clinicaltrials.gov (NCT02624050), and CONSORT guidelines were followed in the design, execution, and reporting of the study. The trial began in August 2016 and terminated in August 2017.

The study was designed as an unblinded, parallel, 2-group (equally-allocated), randomized clinical trial. Patient randomization was stratified by gender (male/female) and use of ACEi versus ARB. A patient sample size of 120 subjects (60 per group, which included a 20% dropout factor) was calculated, which would afford 90% power to detect a difference between the proportion of subjects having at least 1 hypotension episode in the propofol group of 0.85, compared with 0.55 in the methohexital group. ASA class II or III patients taking ACEi or ARB for at least 6 weeks and undergoing elective noncardiac surgery at a tertiary medical center were screened for study inclusion by using their electronic medical record. We excluded patients having a body mass index $>40 \, kg/m^2$, known or suspected difficult airway or intravenous access, requiring preoperative regional anesthetic blockade, and patients with severe cardiac disease (history of decompensated heart failure, uncontrolled arrhythmias, or significant valvulopathy) or renal disease (baseline serum creatinine $>2 \, mg/dL$). All patients were instructed to follow the recommendations provided by the consultant anesthesiologist at the preoperative optimization clinic regarding continuation of ACEi/ARB immediately before surgery. These recommendations were made on an individualized basis and independent of inclusion in this research study.

Study patients were randomized for anesthetic induction using either propofol (Diprivan, Astra-Zeneca, Cheshire, UK) or methohexital (Brevital, Par Pharmaceuticals, NY) (See Supplementary Content for randomization protocol, http://links.lww.com/MD/C796). Patients then underwent a standardized induction protocol with 0.015 mg/kg midazolam, 1 mcg/kg fentanyl, and 1 mg/kg lidocaine, and differing only in the administration of propofol (2.5 mg/kg) or methohexital (1.5 mg/kg) as the induction agent (See Supplementary Material for full protocol, http://links.lww.com/MD/C796). Medication doses used were determined to be equipotent from previous studies.[9,12] Following anesthetic induction, as assessed by loss of eyelash reflex, 0.6 mg/kg rocuronium was administered and anesthesia was maintained with 2% inhaled sevoflurane. Ventilator parameters were standardized by ideal body weight. Intubation was performed by the consultant anesthesiologist exactly 3.5 minutes following administration of propofol or methohexital. No surgical intervention was permitted for 15 minutes after induction.

Blood samples were taken within 1 hour before anesthetic induction (baseline concentration), and at 3, 5, 10, and 15 minutes after anesthetic induction. These samples were analyzed for serum neurohormone concentrations by using enzyme immunoassay (ELISA) kits for arginine vasopressin (Enzo Life Sciences Inc, NY), angiotensin II (RayBiotech Inc, GA), norepinephrine (Abnova, Taipei, Taiwan), and epinephrine (Abnova). Hemodynamic parameters, including blood pressure and HR, were also measured at 1 minute intervals after anesthetic induction for a total of 15 minutes, when the study was terminated.

In order to account for individual differences in baseline blood pressures, hypotension was defined as the greater of the following 2 values:

(1) a systolic blood pressure (SBP) < 85mm Hg, or
(2) a decrease of more than 30% from the individual's baseline SBP.

If the patient developed hypotension within 15 minutes after anesthetic induction, the treatment algorithm outlined in Figure 1 was followed.[10]

2.1. Statistical analysis

Our primary study outcome was the degree of hypotension in patients undergoing anesthetic induction with propofol versus methohexital. Our secondary outcomes were:

(1) total number of vasopressor doses administered (ephedrine, phenylephrine, or arginine vasopressin),
(2) duration of each hypotensive episode,
(3) rate of refractory hypotension (defined as SBP <85 mm Hg following 3 doses of vasopressors),
(4) SBP,
(5) diastolic blood pressure (DBP),
(6) HR, and
(7) blood concentrations of arginine vasopressin, angiotensin II, epinephrine, and norepinephrine (at baseline, and 3, 5, 10, and 15 minutes following anesthetic induction).

For the primary and secondary outcomes, log-binomial regression was used to compare propofol and methohexital groups. Poisson regression was used to compare the number of hypotensive episodes per patient over the first 15 minutes after treatment initiation, with the effect size quantified using a rate ratio.
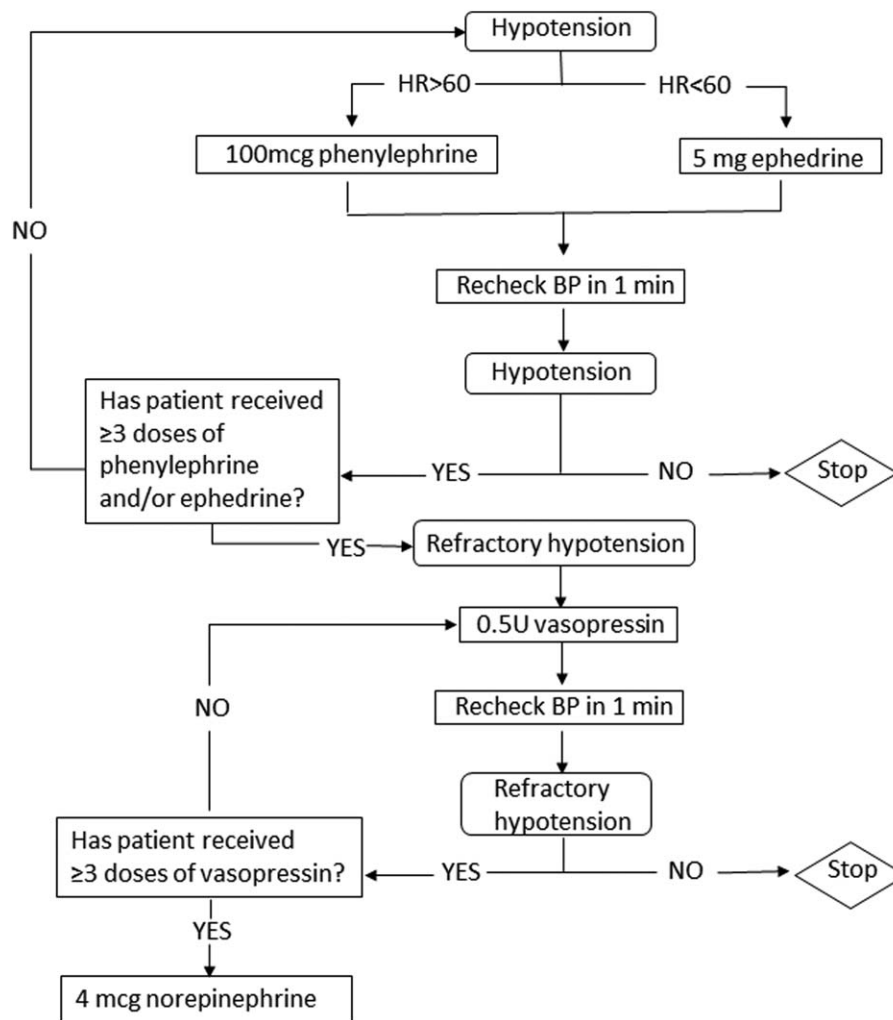
Figure 1. Treatment algorithm for hypotension (defined as SBP <85 mm Hg or >30% decrease from baseline SBP) and refractory hypotension (defined as hypotension despite administration of 3 doses of phenylephrine and/or ephedrine). BP = blood pressure, HR = heart rate, SBP = systolic blood pressure, U = units.

For the secondary hemodynamic outcomes of SBP, DBP, and HR over the first 15 minutes following induction, the area under the curves for each variable was calculated using the trapezoidal rule and compared using 2-sample *t* tests. Two-sample *t* tests were also used to assess differences between the 2 treatment groups with respect to the total number of vasopressor doses and the duration of hypotensive episodes. A general linear model with correlated errors was used to compare the serum concentrations of neurohormones collected over time. The independent variables in the model were treatment arm, time and interaction of treatment with time. *P* was regarded as significant at the .05 level.

3. Results

Demographic and drug dosing information are shown in Table 1. The mean duration since last dose of ACEi and ARB were 24 and 22 hours, respectively. Only 3 patients in each group took their ACEi and ARB within 6 hours of anesthetic induction. Three patients required less than the planned induction dose of methohexital for loss of eyelash reflex, and 2 patients in the methohexital group required additional induction dosing and so were excluded from analysis (Fig. 2).

The analysis demonstrated a significant increase in the degree of hypotension in the propofol group compared with the methohexital group (*P*=.01, Table 2). Furthermore, SBP, DBP, and HR were significantly higher compared to individualized baseline values when methohexital was used for induction (Fig. 3). There was a trend towards more vasopressor use in the propofol group, although this difference did not reach statistical significance in the study population (*P*=.07). There was no significant difference in the number of missing hemodynamic values between randomization groups that would bias the results (average of 11/15 blood pressure readings were obtained over the 15-minute study period in both groups). Nor was there a significant difference in either the absolute serum concentration or the difference from preoperative serum concentrations in any of the neurohormones measured, although there was a nonsignificant trend towards higher epinephrine and norepinephrine concentrations in the methohexital group (Fig. 4).

A planned interim analysis demonstrated significance in our primary objective, but no statistical differences in concentrations of norepinephrine, epinephrine, arginine vasopressin, or angiotensin II, likely due to the substantial variation in plasma levels. The study was stopped at interim analysis due to the high cost of full neurohormonal analysis and a low likelihood of demonstrat-

Table 1

Demographic and drug dosing information for the 45 patients completing the study.

	Methohexital (n=20)	Propofol (n=25)
Male (%)	13 (65)	14 (56)
Age	64 ± 9	60 ± 14
ASA physical status		
Class I (%)	1 (5)	0 (0)
Class II (%)	6 (30)	13 (52)
Class III (%)	12 (60)	12 (48)
Class IV (%)	1 (5)	0 (0)
Mean BMI, kg/m^2	30.4 ± 4.7	30.4 ± 4.7
Mean baseline SBP in mm Hg (±SD)	160 ± 23	159 ± 26
Mean baseline DBP in mm Hg (±SD)	90 ± 11	87 ± 11
Mean baseline HR in mm Hg (±SD)	70 ± 15	71 ± 13
Number of additional blood pressure readings required to determine baseline SBP (%)	5 (25)	2 (8)
Number of patients on		
ACEi (%)	10 (50)	16 (64)
ARB (%)	10 (50)	9 (36)
Mean duration since last dose of ACEi, h	28 ± 25	19 ± 10
Mean duration since last dose of ARB, h	22 ± 9	23 ± 15
Type of ACEi		
Lisinopril (%)	9 (90)	12 (75)
Enalapril (%)	1 (10)	3 (19)
Benazepril (%)	0 (0)	1 (6)
Type of ARB		
Losartan (%)	8 (80)	7 (78)
Valsartan (%)	1 (10)	2 (22)
Olmesartan (%)	1 (10)	0 (0)
Number of patients on concurrent beta blockers (%)	11 (55)	10 (40)
Number of patients on concurrent calcium channel blockers (%)	4 (20)	3 (12)
Mean fentanyl dose at induction, mcg	65.5 ± 12.3	64.6 ± 13.3
Mean lidocaine dose at induction, mg	66.8 ± 10.7	65.8 ± 12.2
Mean midazolam dose at induction, mg	1.02 ± 0.17	1.00 ± 0.17
Mean rocuronium dose at induction, mg	39.5 ± 6.6	39.0 ± 7.5
Mean methohexital dose at induction, mg	125 ± 34	n/a
Mean propofol dose at induction, mg	n/a	194 ± 38

ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASA = American Society of Anesthesiologists, BMI = body mass index, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure, SD = standard deviation.

ing any further significant differences based on our preliminary results.

Forty-five patients completed the study at the time of termination. We examined 3 types of conditional power (ie, the probability that we will find a statistically significant result for the primary outcome at our planned sample size of 120 patients) at the time of interim analysis. Based on our data for the proportion of subjects with at least 1 hypotensive episode, the conditional power is 70% under the null effects, 99% under the current trend effects, and 99% under the hypothesized (ie, alternative) effects. With these high conditional powers, the significant difference in hemodynamics that we observed at interim analysis in all likelihood would hold at study completion.

4. Discussion

This study, performed in patients receiving AAB, demonstrated that methohexital conferred greater hemodynamic stability over the postinduction study period when compared with equi-anesthetic doses of propofol. However, it did not show differing neurohormonal levels to explain this effect. The hemodynamic

data demonstrated a statistically significant difference in the degree of hypotension and HR following anesthetic induction with methohexital. This supports the primary hypothesis of the study: that methohexital retains its cardiostable properties in patients on AAB and thus offers an advantage over propofol for anesthetic induction in these patients. Methohexital thus compares favorably with etomidate, which was also shown to maintain hemodynamic stability better than propofol in patients receiving AAB[13], and may be a viable alternative to etomidate in patients who are at particularly high risk for etomidate-induced adrenal insufficiency.[11]

What remains unexplained is the mechanism for methohexital's hemodynamic stability. Methohexital is reported to sensitize the baroreceptor reflex,[7] which might have been demonstrated by elevated post-induction concentrations of circulating catecholamines. While the measured baseline preoperative concentrations of norepinephrine and epinephrine were consistent with those previously reported in hypertensive patients, there was only a nonsignificant trend towards elevated serum norepinephrine and epinephrine concentrations in patients after methohexital induction. Hence, we can only speculate that methohexital's hemodynamic stability in patients on AAB is conferred through the baroreceptor mechanism as suggested by others.[7,14]

Whether to stop AAB preoperatively in an attempt to avoid perioperative hypotension remains extremely controversial.[4,5,15] Hence, we deferred to the individualized recommendations made by the anesthesia preoperative clinic regarding the continuation of ACEi/ARB or not before surgery (controlled hypertensives are asked to hold administration of a morning dose at our institution). As a result, the majority of our study patients had last taken their antihypertensive within 24 hours of surgery, a time-frame that is well recognized for the continuing pharmacological effects of AAB's.[16,17]

This study should be interpreted within the context of its limitations. First, baseline blood pressure, which was used to define the development of hypotension, was determined before anesthetic induction. This is an approach that has been adopted by others who have studied postinduction hemodynamic variability.[18,19] The alternative could have been the use of outpatient-measured blood pressure as a baseline, which might be regarded as less representative of the patient's hypertensive state at the time of the study intervention. Somewhat validating our approach was the fact that the so measured baseline blood pressures did not differ between study groups after randomization.

Hypotension was defined as SBP <85 mm Hg,[20,21] or a decrease of more than 30% from the individual's baseline SBP.[13,21] While there is more than 1 definition of hypotension, most anesthetic studies use the term to refer to SBP between 80 and 100 mm Hg, or between 70 and 80% of baseline SBP.[22] In light of our unblinded study design, we opted for a more stringent definition to ensure that we avoided treatment bias while remaining within appropriate safety parameters. The disadvantage of this approach may have been under-detection of refractory hypotension which, in our analysis, was deemed not to be statistically different between groups.

Second, we prematurely stopped the study following an interim analysis demonstrating that the primary hypothesis was fulfilled, and bringing into doubt that the neurohormonal analyses (which would incur considerable further costs) could be used to explain the hemodynamic superiority of methohexital when compared with propofol. Ad hoc statistical analyses determined that the
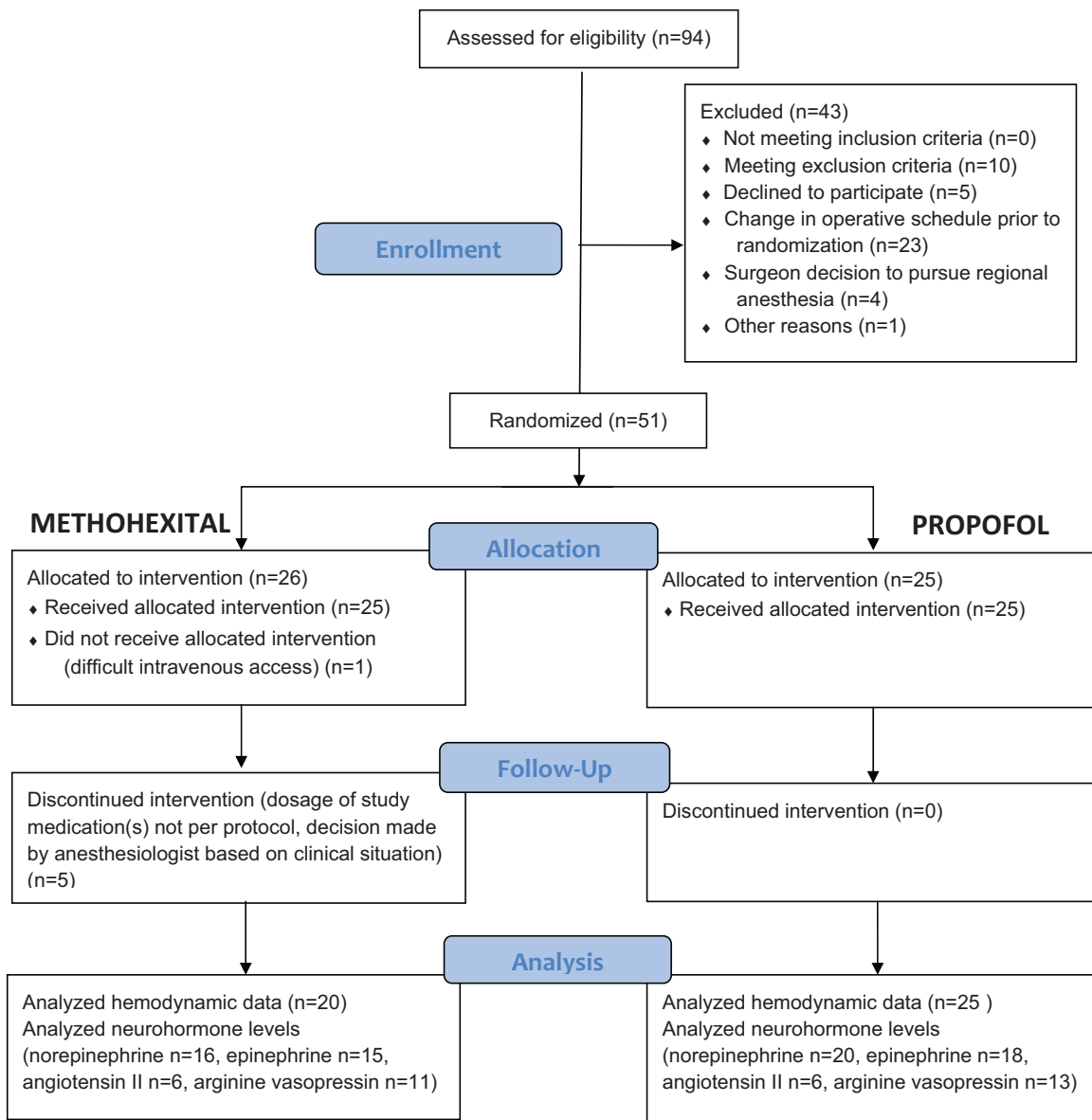
Figure 2. Flow diagram for patient enrollment, allocation, and analysis, per CONSORT 2010 guidelines.

Table 2

Analysis of hemodynamic variables during first 15 min following anesthetic induction with propofol (n = 25) or methohexital (n = 20).

Variable	Propofol	Methohexital	Propofol versus Methohexital Effect Size (95% CI)	P value
Incidence of hypotension, n (%)	21 (84)	8 (40)	2.10 (1.20, 3.69)*	.01
Incidence of refractory hypotension, n (%)	5 (20)	2 (10)	2.00 (0.43, 9.24)*	.37
Degree of hypotension (episodes/min), mean (95% CI)	0.12 (0.08, 0.16)	0.06 (0.04, 0.10)	1.99 (1.11, 3.59)†	.02
Duration of each hypotension episode (min), mean ± SD	4.8 ± 3.4	5.1 ± 3.7	−0.3 (−3.3, 2.7)‡	.83
Doses of Vasopressors, mean ± SD	1.7 ± 1.5	0.9 ± 1.4	0.8 (−0.1, 1.7)‡	.07
AUC of ΔSBP over 15 min (mm Hg × min), mean ± SD	−443 ± 275	−250 ± 289	−193 (−364, −23)‡	.03
AUC ΔDBP over 15 min (mm Hg × min), mean ± SD	−201 ± 105	−60 ± 139	−140 (−214, −67)‡	<.001
AUC ΔHR over 15 min (bpm × min), mean ± SD	64 ± 114	141 ± 119	−76 (−147, −6)‡	.03
Systolic blood pressure averaged over 15 min (mm Hg), mean ± SD	126 ± 22	141 ± 26	−15 (−30, −1.0)‡	.04
Diastolic blood pressure averaged over 15 min (mm Hg), mean ± SD	72 ± 11	85 ± 12	−13 (−20, −6)‡	.001
Heart rate averaged over 15 min (bpm), mean ± SD	76 ± 15	80 ± 14	−4 (−13, 5)‡	.34

AUC = area under the curve, CI = confidence interval, ΔDBP = difference between measured diastolic blood pressure at each time point and baseline diastolic blood pressure, ΔHR = difference between measured heart rate at each time point and baseline heart rate, ΔSBP = difference between measured systolic blood pressure at each time point and baseline systolic blood pressure, SD = standard deviation.

* Effect size = risk ratio from log-binomial model.

† Effect size = rate ratio from Poisson regression model.

‡ Effect size = difference in means from 2-sample t test.
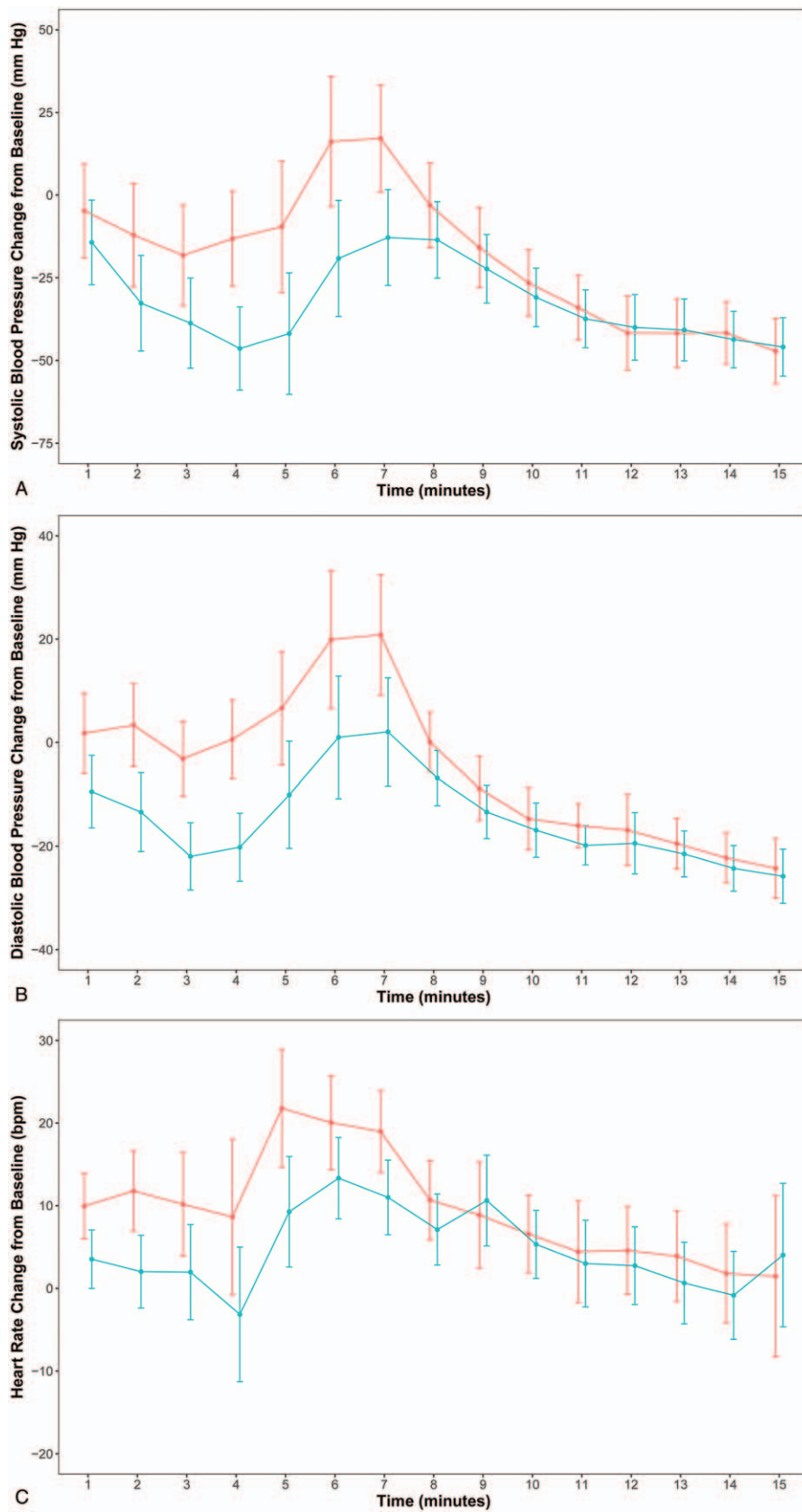
Figure 3. Hemodynamic variables in patients induced with propofol (—●—) and methohexital (—●—); A. Changes in systolic blood pressure with time. B. Changes in diastolic blood pressure with time. C. Changes in heart rate with time.

Figure 4. Serum concentrations of neurohormones during the first 15 minutes following anesthetic induction. The 3-minute time point represents pre-intubation neurohormone levels, while the 5-minute time point represents postintubation neurohormone levels. Vasopressin concentrat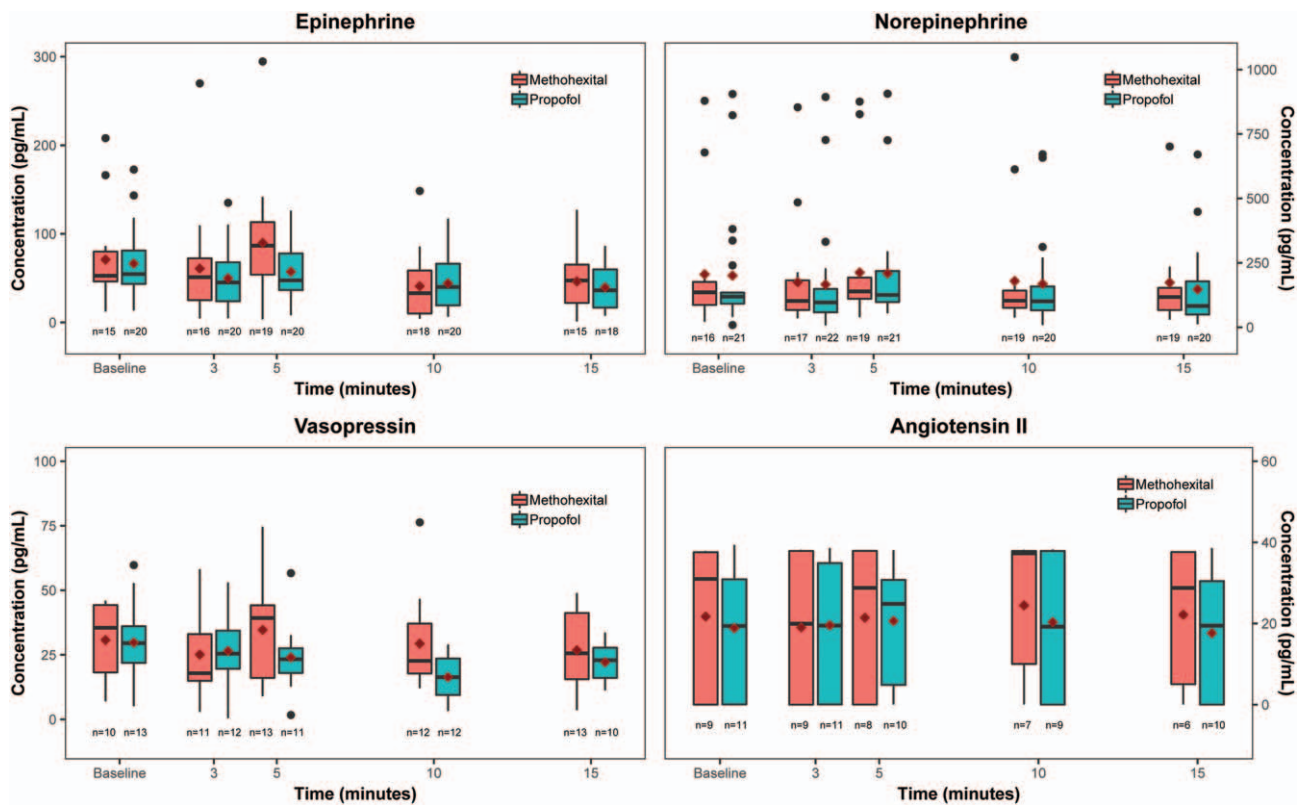ions are shown only for patients who were not treated with intravenous vasopressin as part of the refractory hypotension protocol shown in Figure 1. Red diamond represents mean concentration of respective hormone at that time point.

hemodynamic study findings would likely be maintained with total recruitment of 120 patients. However, in the context of a planned randomized trial, this is an important limitation.

In conclusion, while patients taking ACEi/ARB have altered autonomic and hormonal axes, anesthetic induction with methohexital may preserve hemodynamic stability and mitigate hypotension-related complications in this patient population. However, the results could not confirm a mechanism of methohexital-induced "resetting" of baroreflex sensitivity that has been suggested by others. Nevertheless, the present study has demonstrated that methohexital may be used with advantage as an alternative to propofol to maintain hemodynamic stability after induction in hypertensive patients receiving AAB drugs.

Author contributions

Conceptualization: Anthony Bonavia, Thomas Verbeek, Sanjib Adhikary, Arne Budde, Berend Mets.
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