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General Anesthesia Imposes Negative Effects on Heart Rate and Blood Pressure Regulation in Patients With a History of Head and Neck Radiation Therapy

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Abstract

BACKGROUND: Head and neck radiation therapy (HNRT) impairs baroreflex sensitivity. Therefore, it may potentiate the effects of general anesthesia on heart rate (HR) and arterial blood pressure (BP) regulation during surgery. Currently, the impacts of HNRT on regulation of HR and BP under general anesthesia remain unclear.

METHODS: In this study, 472 patients with primary oral cavity or oropharyngeal cancer at all stages were examined. Half of the patients underwent HNRT plus surgery (treatment group). The other half underwent surgery only and was matched with the treatment patients according to age, sex, and body mass index at a 1:1 ratio (control group). The HR and BP values in the two groups during anesthesia induction, skin incision, and anesthesia emergence were compared retrospectively. A multivariable model of repeated measures with unstructured covariance structure was used to examine the associations of HNRT with intraoperative HRs and BPs after adjusting for baseline HR and BP, time effect, use of β -blockers, history of chemotherapy, and American Society of Anesthesiologists physical status score (ASA scores). BP and HR measurements were collected every 5 minutes. The baseline HR and BP measurements were not included in the outcome vector and were only used as adjustment for the baseline.

RESULTS: Compared with the corresponding baseline values in the controls, the baseline HR was significantly higher ($P = 0.0012$) and the baseline systolic BP was significantly lower ($P < 0.0001$) in the treatment group. The baseline diastolic BP levels did not differ significantly ($P = 0.6411$). Significantly fewer patients receiving HNRT than controls took β -blockers daily (17% versus 28%; $P = 0.0041$). In comparing the corresponding values in the control and treatment groups, multivariable analysis revealed significant associations of HNRT with decreases in HR

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during anesthesia induction (-2.21 [95% confidence interval (CI), -4.42 to -0.01]; $P = 0.0492$) and skin incision (-2.66 [95% CI, -5.16 to -0.16]; $P = 0.0373$) and of HNRT with decreases in systolic BP during anesthesia induction (-6.88 [95% CI, -10.99 to -2.78]; $P = 0.0011$) and skin incision (-15.87 [95% CI, -20.45 to -11.29]; $P < 0.001$). However, we observed a significant association of HNRT with decrease in diastolic BP only during skin incision (-6.50 [95% CI, -9.47 to -3.53]; $P < 0.0001$).

CONCLUSIONS: The most significant finding in the study was that general anesthesia imposed a negative chronotropic effect on the HR in the group given HNRT. Therefore, one should be watchful for bradycardia in these patients; particularly those with low BPs. Their hemodynamic condition may rapidly progress into an unstable status when significant bradycardia and hypotension developing altogether.

Worldwide, more than 650,000 new cases of head and neck cancer are diagnosed each year.¹ Among these patients, 20–30% will have distal metastases in addition to local or regional recurrences.^{2,3} The treatment of advanced head and neck cancer, depending on the subsite of disease, has trended from surgery to radiation therapy or chemoradiation as the initial modality in an attempt to preserve aerodigestive structure and functionality.⁴ Patients with persistent disease after initial treatment or with recurrence may subsequently undergo surgery.

Physicians have long been aware that head and neck radiation therapy (HNRT) impairs sympathovagal balance and carotid sinus baroreflex^{5–8} and therefore influences blood pressure (BP) and heart rate (HR) regulation. Radiation-induced impairment of hemodynamic regulation is a long-term dynamic process. However, most patients suffer only subtle damage to hemodynamic regulation after HNRT, and changes in their BP and HR in response to emotional and/or physical stress are largely regulated. Currently, the long-term impacts of cancer treatments on anesthetic management are largely unknown. General anesthesia has a mixed influence on sympathetic neural outflow and hemodynamic stability. Positive pressure ventilation may activate the sympathetic nervous system to compensate for decreased cardiac filling resulting from positive intrathoracic pressure. On the other hand, intravenous administration of propofol has not only decreased sympathetic nervous system activity but also blunted the HR response to hypotensive challenge.⁹ Volatile anesthetics, except for desflurane which transiently increase sympathetic nervous system activity via a quick concentration surge, decrease peripheral vascular tone and suppress baroreflex responses to hypotension.¹⁰ Therefore, patients who suffer from subtle damage to hemodynamic regulation induced by HNRT may have profound BP and HR changes in response to noxious stimulation under general anesthesia. However, the impacts of HNRT on the regulation of HR and BP under general anesthesia remain unclear.

We retrospectively reviewed a group of patients with oral cavity or oropharyngeal malignancies initially treated with HNRT with or without concurrent chemotherapy and subsequently treated with surgery. We then compared BPs and HRs during anesthesia induction, skin incision, and anesthesia emergence with the corresponding BPs and HRs in patients treated upfront with surgery. Our primary goal was to assess the associations of

general anesthesia with intraoperative hemodynamic measurements in patients with a history of HNRT.

METHODS

Patient Selection

The Institutional Review Board of The University of Texas MD Anderson Cancer Center (UTMDACC) approved this study. Patients were identified by a head and neck surgery registry at UTMDACC including 4011 adults (≥ 18 years of age) who had primary oral cavity or oropharyngeal cancer at all stages. All of the patients underwent surgery under general anesthesia with tracheal intubation from 2007 to 2012. The study exclusion criteria consisted of documented autonomic neuropathy, cardiomyopathy with impaired left ventricular ejection fraction due to any cause (ischemic, nonischemic, and chemotherapy-related factors), concurrent HNRT or chemotherapy at the time of surgery, the presence of an implanted cardiac device (a pacemaker or defibrillator), atrial fibrillation, and fiber-optic airway intubation while awake or asleep.

Of the 4011 patients, 236 (30 female and 206 male) who received intensity-modulated radiation therapy alone or concurrently with chemotherapy before surgery and met our inclusion criteria were identified and placed in the treatment group. Also, 1640 patients (192 female and 1448 male) in the registry who had surgery only and met the inclusion criteria for the study were identified and formed a pool for selection of controls. However, for some of these patients, electronic data on confounding factors potentially related to HR and BP changes, including history of chemotherapy and daily antihypertensive use, were unavailable for retrieval. Therefore, cohort was not readily available for use as a control group, and a control group could not be randomly created without replacement of the missing data. To avoid manual data clarification and replacement for all the patients in the pool, age, sex, and body mass index (BMI) were chosen as matching factors with a ratio of 1:1 to select 236 controls. The missing data on the controls were handpicked from corresponding database including chemotherapy and the list of home medications and placed in the analysis data after matching. The matching range for age was ± 5 years, and the treatment and control groups were matched according to BMI at five levels: up to 25 kg/m², 26–30 kg/m², 31–35 kg/m², 36–40 kg/m² and greater than 40 kg/m². Each patient in the treatment group was successfully matched with a control patient.

Data Collection

Patient characteristics, including age, sex, BMI, American Society of Anesthesiologists (ASA) physical status score, type of daily oral antihypertensive taken (β -blockers versus non- β -blockers), history of chemotherapy, history of HNRT (bilateral versus unilateral), and interval from HNRT to surgery, were collected. Baseline hemodynamic variables for each patient, including systolic BP (SBP), diastolic BP (DBP), and HR measured during preoperative assessment (typically 1–2 days before surgery), were retrieved from the anesthesia database at MD Anderson. Also, all three of these hemodynamic variables collected electronically during surgery at 5-minute intervals were obtained from the same database to obtain the baseline variables. BP values measured using BP cuffs and HR

readings recorded using a pulse oximeter were the primary sources for these variables. Missing BP and HR data were replaced with the nearest available readings at corresponding time points. To avoid the influences of volume shift on the HR and BP changes during surgery, data on hemodynamic variables 30 minutes after anesthesia induction and 15 minutes after first skin incision were collected (significant bleeding is unlikely in this interval). In addition, owing to large variation in hemodynamic changes in response to anesthetic withdrawal, BP and HR data obtained 20 minutes before tracheal extubation were included in the study.

Anesthetic data were not included in our analysis. However, as per our routine practice, the agents typically used for anesthesia induction are propofol and fentanyl; rocuronium (or succinylcholine) is used to facilitate endotracheal intubation. Anesthetic maintenance is achieved with an inhaled agent. For patients undergoing head and neck surgeries, desflurane is the most commonly used inhaled agent in our practice.

Statistical Analysis

Summary statistics were calculated, including mean values, standard deviations, and ranges for continuous variables such as age, BMI, and interval from radiation therapy to surgery. The frequency counts and percentages for categorical variables such as sex and irradiation status were summarized. The Fisher exact test or a chi-square test was used to evaluate associations between two categorical variables. The Wilcoxon rank sum test was used to evaluate differences in continuous variables between patient groups. Mean and standard error plots over time for each BP and HR measurement were generated for the treatment and control groups. A multivariable model of repeated measures was used to examine the associations of HNRT with intraoperative HR and BP after adjusting for baseline HR and BP, the time effect, and other covariates potentially associated with intraoperative HR and BP changes, including use of β -blockers, history of chemotherapy, and ASA score. BP and HR measurements were collected every 5 minutes for 30 minutes during anesthetic induction, for 15 minutes during incision, and for 20 minutes during emergence. Time was treated as a continuous variable in the model. The baseline measurements of BP and HR were not included in the outcome vector and were only used as adjustment for the baseline. Linear mixed effects models with an unstructured covariance structure were used for the BP and HR outcomes. We explored three covariance structures: Unstructured (UN), compound symmetry (CS), and autoregressive (AR (1)), and chose the most appropriate structure to better fit the data. In our analysis, the UN covariance structure had lower values for AIC and BIC compared with CS and AR(1) structures. The interaction between treatment and time was assessed and included in the multivariable model if the interaction was significantly associated with BP or HR. The relationships between treatment and outcomes were assessed by collapsing over time.

All tests were two-sided. *P* values less than 0.05 were considered statistically significant. All analyses were conducted using the SAS (version 9.4; SAS Institute, Cary, NC) and S-Plus (TIBCO Software, Palo Alto, CA) statistical software programs.

RESULTS

In total, we included 472 patient records in our retrospective review. The median age of the patients was 58.7 years (range, 31.0–84.0 years). Half of them received HNRT alone or with concurrent chemotherapy as the initial treatment and subsequently underwent surgery, whereas the other half received upfront surgery. The patient distribution according to sex was equal in the two groups: 30 female (13%) and 206 male (87%) patients. The mean ($\pm$ standard deviation) ages of the patients in the treatment and control groups were 59.1 ± 9.0 years and 58.3 ± 9.2 years, respectively ($P = 0.364$). The mean ($\pm$ standard deviation) BMIs in the treatment and control groups were 25.57 ± 4.66 kg/m² and 25.45 ± 4.40 kg/m², respectively ($P = 0.873$). The standardized differences in age and BMI between the two groups were 8.32% and 7.41%, respectively. We identified no intraoperative mortality or cardiac arrest information in the data.

The distribution of the two groups according to baseline characteristics is presented in Table 1. Compared with the control group, the treatment group had higher overall ASA scores ($P = 0.0412$). Also, 28% of the control patients and 17% of the treatment patients were taking β -blockers ($P = 0.0041$). In addition, 45% of the control patients and 28% of the treatment patients were taking multiple antihypertensives ($P = 0.0001$).

Of the 236 patients with a history of HNRT, 86% underwent chemoradiation, with the remaining 14% undergoing HNRT only. Furthermore, 214 patients (91%) underwent bilateral irradiation, whereas 22 (9%) underwent unilateral treatment. The median interval from irradiation to surgery was 93 days (range, 21–2121 days). Additionally, 39 patients (17%) in the control group received preoperative chemotherapy. Age, sex, and BMI were well balanced between the two groups. We adjusted for the unbalanced covariates, consisting of ASA score, β -blocker use, and history of chemotherapy, in our multivariable model.

The baseline hemodynamic variables in the two groups are summarized in Table 2. In comparing the baseline BPs and HRs in the two groups, we found that the treatment group had a significantly higher mean resting HR ($P = 0.0012$) and significantly lower mean SBP ($P < 0.0001$). However, the difference in mean DBP was not significant ($P = 0.6411$).

Figure 1 shows mean and standard error plots of BP and HR measured in real time in the two patient groups at baseline, anesthesia induction, skin incision, and anesthesia emergence. The P values were based on a model of repeated measures collapsed over time for comparison of the two groups.

During anesthesia induction, the patients in both groups underwent continuous declines in BP during the first 15 minutes after onset of anesthetic induction. Patients given HNRT presented with significantly lower SBPs than did the corresponding control patients ($P < 0.0001$; Column 1 of Figure 1). The DBP values did not differ significantly between the two groups ($P = 0.6382$). The HR values during anesthesia induction also did not differ significantly between the two groups ($P = 0.4732$). All of the patients presented with mild elevations in HR at 5 minutes after anesthesia induction, reflecting HR acceleration due to endotracheal intubation. Whereas the control patients had a mean ($\pm$ standard deviation) HR increase of 4.4 ± 14.1 bpm, the patients given HNRT had a mean ($\pm$ standard deviation) HR

increase of 1.9 ± 12.5 bpm ($P = 0.0474$) indicating that the patients in the treatment group had decreased HR responses to endotracheal intubation. The difference in HR at 5 minutes after anesthetic induction between the groups was -3.0 [95% CI, -5.7 to -0.2].

During incision, the BP readings in the treatment group were significantly lower than those in the control group ($P < 0.0001$ in SBP; $P = 0.0162$ in DBP; Column 2 of Figure 1). The largest BP discrepancy between two groups was at the time of skin incision, indicating that the patients in the treatment group had reduced hypertensive responses to incision. The differences in the HR readings between the two groups were not statistically significant. However, the HRs in the treatment group were below the baseline at all time points, whereas those in the control group were above the baseline during the first 10 minutes.

During emergence from anesthesia, all of the patients had continuous increases in HR and BP toward the time of tracheal extubation, reflecting increased HR and BP responses to anesthesia withdrawal (Column 3 of Figure 1). However, the SBP readings were markedly lower in the treatment group than in the control group at all time points ($P = 0.0066$), whereas DBPs ($P = 0.4711$) and HRs ($P = 0.5113$) did not differ between the two groups.

Use of a mixed model to examine the association of daily antihypertensive use, chemotherapy use, and ASA score respectively with intraoperative HR and BP demonstrated that neither β -blocker nor multiple antihypertensive use daily was significantly associated with HR or BP ($P > 0.05$). The ASA scores and overall effects of chemotherapy on BP and HR during anesthesia were not significant ($P > 0.05$).

We used multivariable mixed models to examine the associations of the treatments (HNRT plus surgery versus surgery alone) with HRs and BPs after adjusting for baseline HR and BP, time, daily β -blocker use, chemotherapy, ASA score, and interaction of time and treatment (if the interaction was statistically significant) (Table 3). HR values were significantly associated with treatment (HNRT plus surgery versus upfront surgery). Patients who received previous HNRT had significant decreases in HR at anesthesia induction (-2.21 [95% CI, -4.42 to -0.01]; $P = 0.0492$) and incision (-2.66 [95% CI, -5.61 to -0.16]; $P = 0.0373$) but did not significantly differ in HR during anesthesia emergence (-3.01 [95% CI, -6.31 to 0.29]; $P = 0.0740$) compared with the patients in the control group. Likewise, the patients who had undergone HNRT had significant decreases in SBP during anesthesia induction (-6.88 [95% CI, -10.94 to -2.78]; $P = 0.0011$) and incision (-15.87 [95% CI, -20.45 to -11.29] but no significant decreases in SBP during anesthesia emergence (-5.42 [95% CI, -10.94 to 0.11]; $P = 0.0547$) compared with the patients in the control group. The association between HNRT and DBP decreases was only significant during incision (-6.50 [95% CI, -9.47 to -3.53]; $P < 0.0001$).

DISCUSSION

Baroreflex sensitivity is directly connected to HR response to arterial pressure changes.^{11,12} HNRT is known to impair baroreflex sensitivity and therefore attenuate neuronal responses to BP and HR changes.¹³ Although full-blown baroreflex failure is rare, decreased baroreflex sensitivity after HNRT is common. Timmers et al.⁷ studied 12 patients who

underwent bilateral neck irradiation and found that all of them had markedly decreased HR responses to phenylephrine challenge. Likewise, Huang et al.¹⁴ studied 89 patients after they underwent neck irradiation and found that none of them had HR responses to deep breathing or the Valsalva maneuver. However, none of the patients in either study presented with daily hemodynamic instability. Applying these findings to our patients who received previous HNRT, although their baseline HR and BP were grossly within normal limits, the significantly increasing baseline HR and decreasing SBP plus markedly few patients taking antihypertensives, including β -blockers, were highly suggestive of pathologic changes in HR and BP regulation. Other authors have reported that patients with compromised baroreflex sensitivity had elevated HR and BP.¹⁵ However, our patients presented with increased HR but decreased SBP. We speculate that hypovolemic hypotension resulting from poor oral intake due to pain or difficulty swallowing was the cause of the SBP differences between our patients and the patients in their study. Indeed, both clinical reports^{6,8,12} and our experience indicated that lightheadedness or dizziness and orthostatic hypotension are common in patients with a history of HNRT. The BP changes due to reduced baroreflex sensitivity in the present study were likely superseded by hypovolemic hypotension in patients who underwent HNRT. However, regardless of the reason, preoperative hypotension markedly decreased the tolerance to anesthetics in patients with a history of HNRT.

While the impact of HNRT on baroreceptor sensitivity is generally accepted, the effects of HNRT on hemodynamic stability under general anesthesia is less clear; identifying this impact was the impetus for this study. We found that compared with BP changes in the controls, patients who had history of HNRT presented with significant intraoperative hypotension. Although differences in the measured HRs between the two groups was not statistically significant, HRs in the patients with a history of HNRT decreased significantly from baseline, indicating that anesthetics impose not only hypotensive but also negative chronotropic effects on patients with a history of HNRT. Furthermore, that significantly fewer patients in the treatment group than in the control group took β -blockers supported that the negative chronotropic effect did not result from daily pharmacologic management but rather from organic injuries. Most anesthetics attenuate baroreflex in a dose-dependent manner by interfering with sympathetic neural outflow.^{16,17} However, the depressive effects on baroreflex of anesthetics should be only partial, as the coupling of baroreceptor stimulation and effector responses is grossly maintained under general anesthesia in patients treated with HNRT.¹⁸ Just as we observe decreased HR in response to administration of a phenylephrine bolus and increased HR after increased blood loss during anesthesia in patients with an intact baroreflex, we expect to see some interplay between HR and BP changes during noxious stimulations such as endotracheal intubation and skin incision. Overall negative chronotropic HR responses and a lack of corresponding BP elevation in response to noxious stimulation in patients given HNRT were highly suggestive of impairment of baroreflex-mediated sympathetic cardiac acceleration and sympathetic muscle nerve activity in a previous study.¹⁶ Decreases in HR and BP in addition to lack of appropriate hemodynamic responses to surgical stimulation or volume changes in a patient with pre-existing hypovolemia during anesthesia may quickly result in sustained hypoperfusion. Indeed, others have reported severe hypotension and bradycardia or cardiac arrest under general anesthesia in this population.^{19,20}

The most significant finding in our study was that general anesthesia induced a significant negative chronotropic effect on HR in patients with a history of HNRT. This was seen during anesthetic induction and skin incision, when HRs in the treatment group generally remained below baseline, whereas those of the control group remained above baseline. Although autonomic neuropathy and baroreflex damage are different clinical entities, in our study, the BP and HR changes during anesthesia in patients given HNRT were similar to the hemodynamic responses to anesthesia typically seen in patients with diabetic autonomic neuropathy. Given their impaired autonomic HR and BP regulation, diabetic patients are prone to development of intraoperative hypotension as well as bradycardia.^{21,22} Therefore, the strategies used for perioperative hemodynamic management in diabetic patients may also be effective in patients given HNRT.

The significant impact of general anesthesia on hemodynamic stability through a negative chronotropic effect in patients who underwent HNRT should heighten anesthesia providers' awareness and make one prepared for rapid development of significant bradycardia in this population, particularly those with low BPs. Earlier intervention for bradycardia may prevent development of hemodynamic instability following severe bradycardia.

Because cancer therapies are highly patient-selective, we could not randomly assign our patients to different treatment groups. In addition, owing to the uneven distribution of confounding factors in our relatively small sample size, we could not always appropriately manage the bias due to treatment indications and subject distributions to produce a valid comparison between the two groups.

In summary, the most significant finding in our study was that anesthetics imposed a significant negative chronotropic effect on HR in patients with a history of HNRT. Preoperative hypovolemia exacerbates the hypotensive effects of general anesthesia in this population. When significant bradycardia and hypotension arise altogether, substantial hemodynamic deterioration may develop rapidly. Therefore, one should be watchful for bradycardia in patients who had undergone HNRT, particularly those with concurrent low BPs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Mean and standard error plots of real-time measured BP and HR values at each measurement time point in the two patient groups. The red dots and blue triangles near the left vertical axes are the baseline SBP, DBP, and HR values in the control and treatment groups, respectively. The red and blue lines are the BP and HR change respectively at each time point during the corresponding events in the two groups. Anesthesia emergence (20

minutes) ended at tracheal extubation. The P values were based on the model of repeated measures collapsed over time for comparison of the two groups. Std Err = standard error.

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Table 1:

Distribution of the Two Patient Groups According to Sex, Baseline Physical Conditions, and Treatment Characteristic

Covariate	N (%)		Standardized difference (%)	P
	Control	HNRT		
Sex			0	1.0000
Female	30 (13)	30 (13)		
Male	206 (87)	206 (87)		
ASA score			22.94	0.0412
2	67 (28)	47 (20)		
3	168 (71)	185 (78)		
4	1 (1)	4 (2)		
β-blockers			26.63	0.0041
No	170 (72)	196 (83)		
Yes	66 (28)	40 (17)		
Multiple antihypertensives			35.69	0.0001
No	129 (55)	169 (72)		
Yes	107 (45)	67 (28)		
Chemotherapy			191.1	<0.0001
No	197 (83)	34 (14)		
Yes	39 (17)	202 (86)		
HNRT			N/A	N/A
Bilateral	--	214 (91)		
Unilateral	--	22 (9)		

Table 2.

Comparison of Baseline SBP, DBP, and HR in the Two Patient Groups

Variable	Control	Treatment	<i>P</i> *
	Mean ± std, median (range)	Mean ± std, median (range)	
Baseline SBP (mm Hg)	133.8 ± 25.5, 134 (78–214)	124.7 ± 21.8, 122 (83–203)	<0.0001
Baseline DBP (mm Hg)	70.6 ± 15.5, 70 (30–153)	70.9 ± 11.4, 71 (43–109)	0.6411
Baseline HR (bpm)	71.2 ± 13.9, 70 (40–145)	75.2 ± 13.8, 73 (48–132)	0.0012

std: standard deviation;

* Wilcoxon rank sum test.

Table 3.
Multivariable Analysis of the Association between HNRT and BP and HR after Adjusting for Confounding Factors

SBP			SBP Induction			SBP Incision			SBP Emergence		
Covariate	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate
Treatment (HNRT vs. Control)	-6.88	(-10.99, -2.78)	0.0011	-15.87	(-20.45, -11.29)	<0.001	-5.42	(-10.94, 0.11)	0.0547		
SBP baseline	0.35	(0.29, 0.42)	<0.001	0.15	(0.09, 0.22)	<0.001	0.13	(0.04, 0.21)	0.0031		
Time	-1.32	(-1.84, -0.79)	<0.001	-1.98	(-2.79, -1.18)	<0.001	-6.74	(-7.43, -6.05)	<0.001		
Beta Blocker Use (Yes vs. No)	0.18	(-3.74, 4.10)	0.9275	2.46	(-1.11, 6.03)	0.1756	3.56	(-1.53, 8.65)	0.1700		
Chemotherapy (Yes vs. No)	-0.31	(-4.52, 3.89)	0.8831	-0.69	(-4.45, 3.08)	0.7208	-0.59	(-6.11, 4.93)	0.8337		
ASA (¾ vs. 2)	3.92	(0.44, 7.41)	0.0275	1.96	(-1.36, 5.28)	0.2455	3.48	(-0.43, 7.39)	0.0810		
Time and Treatment Interaction			0.9194*	0.70	(0.37, 1.02)	<0.001			0.1893*		
DBP			DBP Induction			DBP Incision			DBP Emergence		
Covariate	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate
Treatment (HNRT vs. Control)	-1.12	(-3.62, 1.37)	0.3760	-6.50	(-9.47, -3.53)	<0.001	-1.52	(-5.57, 2.53)	0.4602		
DBP baseline	0.37	(0.30, 0.45)	<0.001	0.21	(0.14, 0.28)	<0.001	0.18	(0.10, 0.27)	<0.001		
Time	-1.20	(-1.50, -0.89)	<0.001	-1.60	(-2.07, -1.12)	<0.001	-2.50	(-2.90, -2.11)	<0.001		
Beta Blocker Use (Yes vs. No)	-1.75	(-4.18, 0.67)	0.1563	-0.30	(-2.50, 1.89)	0.7860	0.71	(-2.45, 3.87)	0.6589		
Chemotherapy (Yes vs. No)	0.64	(-1.86, 3.15)	0.6137	1.94	(-0.59, 4.47)	0.1321	1.02	(-2.86, 4.89)	0.6055		
ASA (¾ vs. 2)	0.53	(-1.64, 2.71)	0.6301	-1.88	(-4.10, 0.33)	0.0959	-0.37	(-2.74, 2.01)	0.7611		
Time and Treatment Interaction			0.4719*	0.34	(0.15, 0.53)	0.0005			0.5899*		
HR			HR Induction			HR Incision			HR Emergence		
Covariate	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate
Treatment (HNRT vs. Control)	-2.21	(-4.42, -0.01)	0.0492	-2.66	(-5.16, -0.16)	0.0373	-3.01	(-6.31, 0.29)	0.0740		
HR baseline	0.60	(0.50, 0.69)	<0.001	0.41	(0.33, 0.49)	<0.001	0.29	(0.14, 0.44)	0.0001		
Time	-0.98	(-1.22, -0.74)	<0.001	-0.96	(-1.33, -0.59)	<0.001	-3.25	(-3.61, -2.88)	<0.001		

SBP	SBP Induction			SBP Incision			SBP Emergence		
	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P	Estimate	95% CI of Estimate	P
Covariate									
Beta Blocker Use (Yes vs. No)	-2.65	(-4.66, -0.64)	0.0099	-3.34	(-5.63, -1.03)	0.0045	-1.69	(-4.59, 1.21)	0.2534
Chemotherapy (Yes vs. No)	2.01	(-0.23, 4.25)	0.0785	1.72	(-0.84, 4.28)	0.1884	2.58	(-0.60, 5.76)	0.1112
ASA (¾ vs. 2)	0.18	(-1.78, 2.13)	0.8590	-1.34	(-3.86, 1.17)	0.2943	0.10	(-2.94, 3.15)	0.9471
Time and Treatment Interaction			0.9734*			0.1232*			0.3824*

CI = confidence interval

* The interaction between time and treatment was not significant and not included in the final multivariable model of repeated measures.

BP/HR measurements were collected every 5 minutes for 30 minutes during induction, for 15 minutes during incision, and for 20 minutes during emergence. Time was treated as a continuous variable in the model. The estimate for time was the estimated slope for the combined groups during the respective time period.