Reports of Investigation

Heart rate and blood pressure power spectral analysis during calcium channel blocker induced hypotension

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Purpose: To observe heart rate (HRV) and blood pressure variability (BPV) as indices of neurocirculatory responses to induced hypotension with diltiazem and/or nicardipine for hip surgery.

Methods: Thirty-six ASA I-II patients received diltiazem (group D, n = 12), nicardipine (group N, n = 12) or combination of diltiazem/nicardipine (group DN, n = 12). The intensity of HRV and BPV, was determined by spectral analysis of HRV and BPV before anesthesia (T0), just before induced hypotension (T1), and at 10 and 30 min after the start of induced hypotension (T2 and T3, respectively). The logarithmic HRV and BPV were integrated: sympathetic and parasympathetic mediated low frequency area (0.06-0.1 Hz, LF), parasympathetic related high frequency area (0.15-0.4 Hz, HF) and total frequency area (0.01-0.4 Hz). Blood loss was assessed by weighing gauzes and measuring suction.

Results: Group DN had less blood loss (466 ± 46 ml, mean ± SEM) than group D (733 ± 100 ml, $P < 0.05$). Diltiazem (11.4 ± 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and combination of diltiazem (0.25 ± 0.01 $mg \cdot kg^{-1}$) and nicardipine (5.9 ± 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased LF-HRV at T2 and T3 ($P < 0.05$ *vs* T0 and T1), while nicardipine (8.1 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) showed increase in LF-HRV at T2 ($P < 0.05$ *vs* T1). HF-HRV unchanged through hypotension except for a decrease in group N at T3 ($P < 0.05$ *vs* T1). There were no increases in HF-BPV, and LF-BPV, except for a diltiazem induced decrease in LF-BPV at T3 ($P < 0.05$ *vs* T0 and T1).

Conclusion: Group D and group DN can be used for deliberate hypotension without an increase in sympathetically mediated LF-HRV.

Objectif : Observer la variabilité de la fréquence cardiaque (VFC) et de la tension artérielle (VTA) en tant qu'indices des réponses neurocirculatoires à l'hypotension contrôlée avec le diltiazem et/ou la nicardipine lors d'une opération de la hanche.

Méthode : Trente-six patients ASA I-II ont reçu du diltiazem (groupe D, n = 12), de la nicardipine (groupe N, n = 12) ou une combinaison des deux (groupe DN, n = 12). L'intensité de la VFC et de la VTA a été déterminée par une analyse spectrale de VFC et de VTA avant l'anesthésie (T0), juste avant l'induction de l'hypotension (T1) et à 10 et à 30 min après le début de l'hypotension provoquée (T2 et T3, respectivement). Les logarithmes de VFC et VTA ont été intégrés : zone de basses fréquences d'origine sympathique et parasympathique (0,06-0,1 Hz, BF), zone de hautes fréquences reliée au système parasympathique (0,15-0,4 Hz, HF) et zone incluant toutes les fréquences (0,01-0,4 Hz). La perte sanguine a été évaluée en pesant les compresses et en mesurant le volume aspiré par succion.

Résultats : Dans le groupe DN, la perte sanguine a été moindre (466 ± 46 ml, moyenne ± erreur type) que dans le groupe D (733 ± 100 ml, $P < 0,05$). Le diltiazem (11,4 ± 0,9$\mu g \cdot kg^{-1} \cdot min^{-1}$) et une combinaison de diltiazem (0,25 ± 0,01 $mg \cdot kg^{-1}$) et de nicardipine (5,9 ± 0,9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) ont réduit la VFC-BF à T2 et à T3 ($P < 0,05$ *vs* T0 et T1), tandis que la nicardipine (8,1 ± 0,8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) a haussé la VFC-BF à T2 ($P < 0,05$ *vs* T1). La VFC-HF n'a pas changé pendant l'hypotension sauf pour une baisse chez les patients du groupe N à T3 ($P < 0,05$ *vs* T1). Dans le groupe D, il n'y a pas eu d'augmentation de VPS-HF et la VPS-BF a baissé à T3 ($P < 0,05$).

Conclusion : Les groupes D et DN peuvent servir de modèles dans le cas d'une hypotension contrôlée sans augmentation de la VFC-BF d'origine sympathique.

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INDUCED hypotension has proved to be effective in decreasing both blood loss and requirement for blood transfusion, and providing better visibility in the surgical field. Calcium channel blockers with potent direct vasodilating effects and ease of administration may be advocated for induced hypotension in major hip surgery.[2–4] Nicardipine, a dihydropyridine calcium channel blocker, exhibits potent artery vasodilatation with limited negative inotropic and chronotropic effects.[5] Diltiazem also results in peripheral vasodilatation, with negative chronotropic properties.[6,7] However, there are scant data whether calcium channel blocker alter sympatho-vagal tones during induced hypotension.

Short term fluctuations of heart rate and blood pressure reflect the dynamic responses of the cardiovascular control system to naturally occurring physiological perturbations.[8] Power spectral analysis of these variabilities has recently provided an accurate method to describe and quantify these perturbations. Observations that these variabilities are associated with changes in the sympatho-vagal balance have led to the use of this method as a marker of autonomic tone.[8,9] Spectral analysis of heart rate variability (HRV) suggests that parasympathetic nervous system is mainly responsible for the high frequency spectral component whereas both sympathetic and parasympathetic activities contribute to low frequency power.

The purpose of this study was to determine whether diltiazem and/or nicardipine induced hypotension alter HRV and blood pressure variability (BPV) as indices of the sympatho-vagal responses to deliberate hypotension.

Materials and methods

This study was approved by the local review board. After written informed consent was obtained, 36 adult patients, ASA physical status I or II, scheduled for elective hip surgery were enrolled. Patients with cardiovascular, renal, hepatic,diabetic or neurological disease and those taking antiarrhythmic agents were excluded. Patients were randomly assigned to receive diltiazem (n = 12), nicardipine (n = 12) or diltiazem and nicardipine in combination (n = 12). The ECG (M1002A, Hewlett-Packard, San Francisco, CA) was monitored using standard limb leads (II). Blood pressure was continuously measured by a noninvasive tonometric instrument (CBM7000, Colin Corporation, Komaki, Japan) before induction of anesthesia. After anesthetic induction, the radial artery was cannulated with an indwelling Teflon 20-G intraarterial cannula for continuous monitoring of arterial blood pressure. Pulse oximeter (M1020A, Hewlett-Packard, San Francisco, CA) was used throughout anesthesia. The patients were premedicated with 1 $mg \cdot kg^{-1}$ hydroxyzine *im* at 30 min before induction of anesthesia. Anesthesia was induced with 5 $mg \cdot kg^{-1}$ thiamylal sodium *iv* followed by 1 $mg \cdot kg^{-1}$ succinylcholine *iv* to facilitate tracheal intubation. The minute ventilation was adjusted to maintain at end-tidal CO_2 partial pressure between 30 and 35 mmHg, with a respiratory rate of 14 breaths/min and an I/E ratio of 1:2. Anesthesia was maintained with nitrous oxide 67% and sevoflurane at end-tidal concentration of 2 vol% in oxygen, with incremental doses of 2-3 mg vecuronium for muscle relaxation, as required. Opioids were given through the epidural catheter, after measurement of HRV and BPV, for postoperative analgesia. End-tidal anesthetic concentrations were measured by an anesthetic gas monitor (1304, Brüel & Kjær, Copenhagen, Denmark). Sevoflurane was discontinued at the end of surgery. Arterial pH,$PaO_2$and $PaCO_2$ were measured using a blood gas analyzer (ABL300, Radiometer, Copenhagen, Denmark) at 30 min after the start of hypotension. Changes in heart rate (HR) and mean arterial blood pressure (MAP) were calculated as percentages of baseline values during hypotension to demonstrate the time-course of the effects of induced hypotension on HR and MAP.

Deliberate hypotension was started at 20 min after surgical incision. Initially, a loading dose of 0.2 $mg \cdot kg^{-1}$ diltiazem (diltiazem group and combination group) or 0.02 $mg \cdot kg^{-1}$ nicardipine (nicardipine group) was infused through a Teflon antecubital cannula used only for this purpose.[2,10] In the nicardipine group and the combination group, according to the result of the Wallin *et al.* studies,[11,12] the infusion was started at a rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and continued until MAP was at 60-75 mmHg, at which time the initial infusion rate was reduced. With diltiazem, the infusion was started at a rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and was continued until MAP was 60-75 mmHg according to the results of Bernard *et al.*[2] The initial loading doses and the continuous infusion rates of diltiazem or nicardipine were titrated according to the arterial blood pressure response to each calcium channel blocker. Maintenance doses were administered until muscle and skin closure were started. Blood loss volume was estimated by weighing gauzes and measuring suction drainage. The surgeons were unaware of the type of vasodilator used.

Power spectral analysis of the beat-to-beat heart rate and arterial blood pressure signals have been described elsewhere.[13,14] Briefly, electrocardiographic RR intervals were measured from the ECG monitor. The R wave was detected from the ECG signal with a 17 Hz active band-pass filter, and used as a trigger signal to generate

TABLE Clinical characteristics and procedural summary for 36 patients undergoing hip surgery

	Nicardipine (n=12)	*Diltiazem (n=12)*	*Combination (n=12)*
Age (yr)	50 ± 3	41 ± 3	44 ± 4
Sex (M/F)	2/10	2/10	3/9
Weight (kg)	52 ± 1	56 ± 3	54 ± 2
Operation			
Rotatory acetabular osteotomy	5	9	7
Total hip arthroplasty	7	3	5
Operative time (hr)	2.1 ± 0.09	2.5 ± 0.18	2.4 ± 0.20
Estimated Blood loss (ml)	546 ± 105	733 ± 100	466 ± 46*
Patients receiving autologous blood	7	9	2*
Initial bolus dose of the hypotensive agent ($mg \cdot kg^{-1}$)	0.03 ± 0.003	0.17 ± 0.01	0.25 ± 0.01
Maintenance Infusion rate of the hypotensive agent ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	8.1 ± 0.8	11.4 ± 0.9	5.9 ± 0.9
Cumulative dose of the hypotensive agent ($mg \cdot kg^{-1}$)	0.54 ± 0.05	0.84 ± 0.06	0.31 ± 0.03
Duration of vasodilator administration (min)	69 ± 5	66 ± 6	57 ± 3
Atrioventricular block	0	3	1

M, male; F, female.

Mean ± SEM, or number.

* $P < 0.05$ *vs* Diltiazem

a train of rectangular impulses. The intervals of rectangular impulses were counted successively with a universal counter (UCM-439BPC, Microscience Co. Ltd., Tokyo, Japan), and were stored in the computer (PC9801, NEC, Tokyo, Japan). Instantaneous heart rate was calculated every 250 msec for 320 sec by the method described by de Boer,[15] and filtered < 0.5 Hz with a digital filter. Each 128-sec epoch was analyzed with a fast Fourier transform using a windowed periodgram technique, and the squared magnitude, termed power spectral density, computed.[16] Power spectra of HRV were updated every 32 sec. Averaged power spectra of HRV were calculated from seven sets of power spectral HRV data. To confirm a normal distribution, log power spectra were calculated by taking the common logarithm of the power spectra of each component and total power. The integrated areas of the power spectral peaks within each measurement were divided as follows: sympathetic and parasympathetic related low- (LF-HRV: 0.06-0.10 Hz), parasympathetic related high- (HF-HRV: 0.15-0.4 Hz), and the total-frequency area (0.01-0.4 Hz).[17] Analog output of arterial pressure wave was digitized at 100 Hz by an analog-digital converter (ADJ98, Canopus, Kobe, Japan). The mean value of arterial pressure was obtained following the moving average over 0.5 sec which meant low-pass filtered < 1 Hz, and updated every 250 msec. Each spectral component of BPV was calculated as in HRV analysis. Hemodynamic, HRV and BPV measurements were performed before induction of anesthesia (T0), just before hypotension (T1), and at 10 min and 30 min after the beginning of vasodilator infusion (T2 and T3, respectively).

Statistical significance of differences among the three groups were assessed using Fisher's exact test for binomial data (sex) and unpaired t-tests for continuous data (demographic data, operative time, blood loss and duration of vasodilator administration). Chi-square test was used to compare occurrence rates of dysrhythmias and the incidence of autologous blood transfusion. Comparisons were made by two-way analysis of variance for repeated measurements when the two factors were treatment (nicardipine, diltiazem and their combination) and time, followed by t-test with Bonferroni corrections. Significance was assumed at a P value of 0.05 or less. Data are presented as mean ± SEM.

Results

Clinical characteristics and procedural summary are listed in Table. No differences were observed among groups with respect to age, sex, weight, operative time, duration of vasodilator administration and incidence of atrioventricular block. Intraoperative blood loss of the combined therapy group was less than that of the diltiazem group (P=0.024). End-tidal anesthetic concentration of sevoflurane was adjusted to 2% throughout the measurements, except in one patient

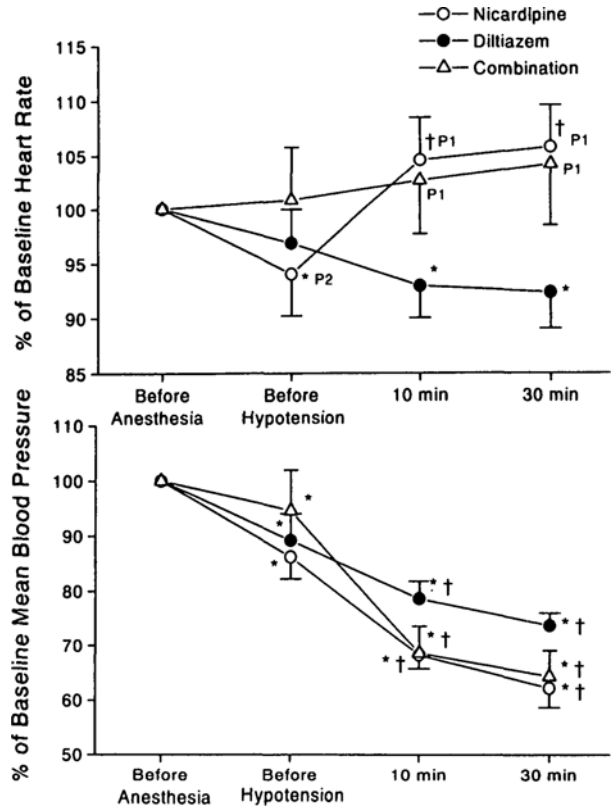

FIGURE 1 Changes in heart rate and mean blood pressure expressed as a percentage of baseline values of the three groups. * $P < 0.05$ *vs* before Anesthesia. † $P < 0.05$ *vs* before Hypotension.
P1 $P < 0.05$ *vs* Diltiazem. P2 $P < 0.05$ *vs* Combination.
Error bars denote SEM.

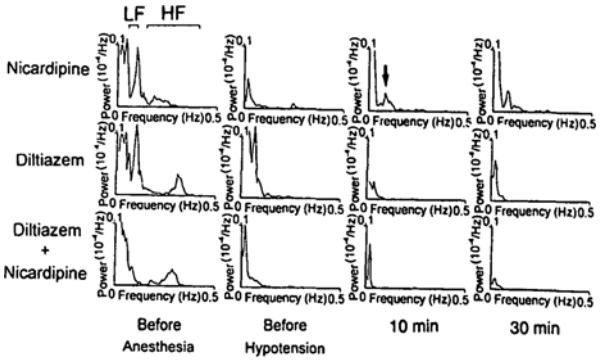

FIGURE 2 Typical power spectral change of heart rate variability (HRV) in patients receiving nicardipine (56 yr, female), diltiazem (33 yr, female) and combination (38 yr, female). In each panel, power spectra of HRV (10^{-4}·Hz^{-1}) plotted up to the frequency of 0.5 Hz. Note the power spectral peak in the low range below 0.2 Hz (LF: low frequency) and the respiratory peak located at the frequency of breathing (HF: high frequency) in the upper left panel. Both diltiazem and combination groups did not show remarkable HRV changes during hypotension. The arrow marks the increased LF-HRV 10 min after the administration of nicardipine.

in the nicardipine group (2.5%), two patients in the diltiazem group (2.5% and 1.5%) and two patients in the combined therapy group (1.5%).

There were no differences in baseline data of HR and MAP: 77 ± 3 bpm and 103 ± 5 mmHg (nicardipine group), 79 ± 3 bpm and 97 ± 3 mmHg (diltiazem group), and 68 ± 3 bpm and 98 ± 8 mmHg (combination group), respectively. The percentages of the baseline values of HR and MAP are shown in Figure 1. Diltiazem led to a decrease in HR to 93 ± 3% at T2, and 92 ± 3% at T3 ($P < 0.05$ *vs* T0), indicating a tendency to decrease HR. On the contrary, nicardipine resulted in an increase in HR to 105 ± 4% at T2 and 106 ± 4% at T3 ($P < 0.05$ *vs* T1). In the combined therapy group HR was unchanged throughout the study. The three study groups showed decreases in MAP at T1 ($P < 0.05$ *vs* T0), T2 and T3 ($P < 0.05$ *vs* T0 and T1).

Figure 2 shows illustrative samples of power spectra of HRV during baseline recordings and deliberate hypotension. In the nicardipine group, spectral peak of LF-HRV increased at T2 slightly as indicated by the arrow in Figure 2. There were no differences among the three groups with respect to baseline data of HRV values (Figure 3). In all study groups, LF-HRV, HF-HRV and total-frequency HRV decreased compared with T0. In the diltiazem and combined therapy groups, LF-HRV decreased at T2 and T3 ($P < 0.05$ *vs* T0 and T1). With nicardipine, LF- HRV increased at T2 transiently ($P < 0.05$ *vs* T1) and decreased at T3 again. In the three groups HF-HRV decreased at T1, T2 and T3 ($P < 0.05$ *vs* T0). The HF-HRV was unchanged during hypotension except for a decrease in group N at T3 ($P < 0.05$ *vs* T1).

Figure 4 shows typical changes of BPV in the three groups. In each group, HF-BPV increased during anesthesia, while LF-BPV decreased. Changes of BPV are summarized in Figure 5. The LF-BPV and total-frequency BPV were decreased by anesthesia itself as was HRV. The HF-BPVs did not change throughout hypotension in any group. During hypotension, changes of LF-BPV and total frequency BPV were unremarkable, except for a decrease in LF-BPV at T3 ($P < 0.05$ *vs* T1) and increase in total frequency of BPV at T2 in nicardipine group ($P < 0.05$ *vs* T1).

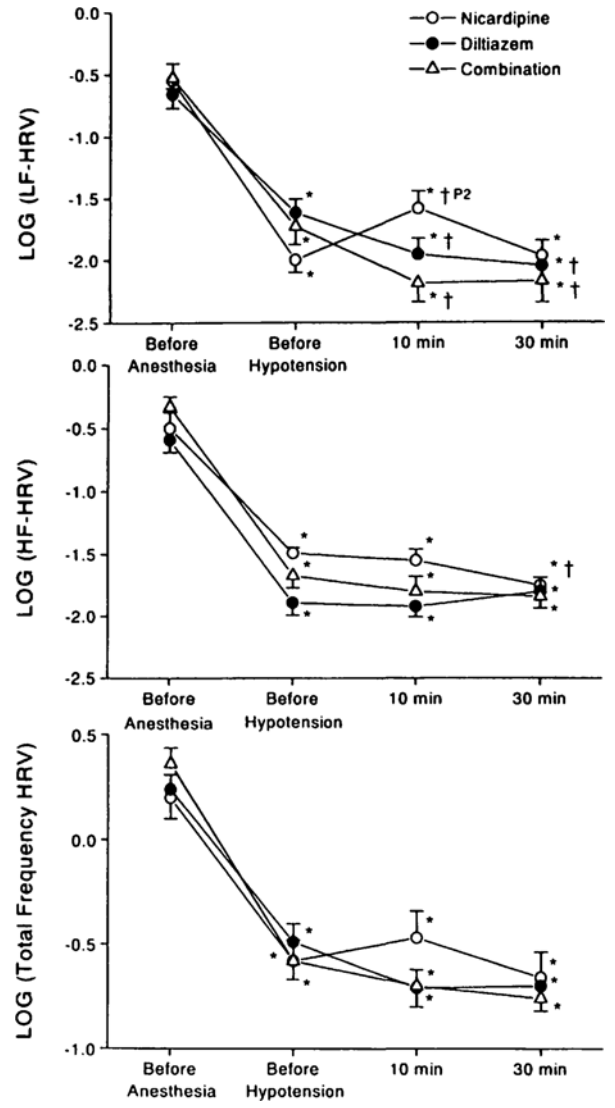

FIGURE 3 Logarithmic change in heart rate variability (HRV) after administration of nicardipine, diltiazem or combination of nicardipine and diltiazem.
* $P < 0.05$ *vs* Before Anesthesia. † $P < 0.05$ *vs* Before Hypotension.
P2 $P < 0.05$ *vs* Combination.
Error bars denote SEM.

One patient in the combined therapy group showed atrioventricular conduction block at 20 min after the start of hypotension, and dysrhythmia reverted spontaneously to sinus rhythm. Three patients in the diltiazem group were given 0.5 mg atropine *iv* for treatment of atrioventricular dissociation, after the measurement of HRV and BPV, which returned to normal sinus rhythm.

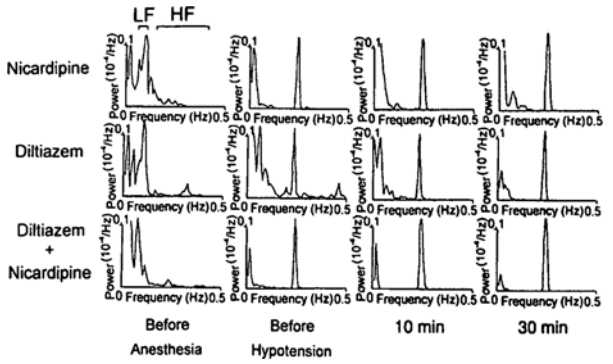

FIGURE 4 Typical power spectral change of blood pressure variability (BPV) in patients receiving nicardipine, diltiazem and their combination. Each patient is the same as in Figure 2. In each panel, power spectra of BPV (10^{-4}·Hz^{-1}) plotted up to the frequency of 0.5 Hz. Note the power spectral peak in the low range below 0.2 Hz (LF: low frequency) and the respiratory peak located at the frequency of breathing (HF: high frequency) in the upper left panel.

Discussion

Few data exist on the acute effects of intravenously administered calcium channel blockers on HRV and BPV. In the current study, LF-HRV showed characteristic changes related to each calcium channel blocker. Nicardipine increased LF-HRV at T2 while diltiazem alone and the combination of diltiazem and nicardipine decreased LF-HRV at T2 during general anesthesia with sevoflurane. The different alterations in LF-HRV to induced hypotension implies that diltiazem blunts initial sympathetic activation arising from baroreflex response to induced hypotension. The negative chronotropic action of diltiazem, therefore, may mask the reflex increase in HR when arterial blood pressure decreases after intravenous administration of nicardipine.

Previous studies concerning effects of chronic administration of diltiazem on HRV are inconsistent and controversial. Cook *et al.* reported a lack of any effects of diltiazem on HRV,[18] whereas other previous studies have shown that diltiazem decreases LF-HRV, and increases HF-HRV.[19,20] These controversies may occur as a result of different clinical settings such as the route of administration, surgical intervention, general anesthesia, and previous cardiovascular complications. In the current study, we examined their use for acute, induced hypotension.

Nicardipine exhibits potent peripheral vasodilatation while maintaining cardiac contractility and cardiac output.[10] In contrast, diltiazem alone has been reported to

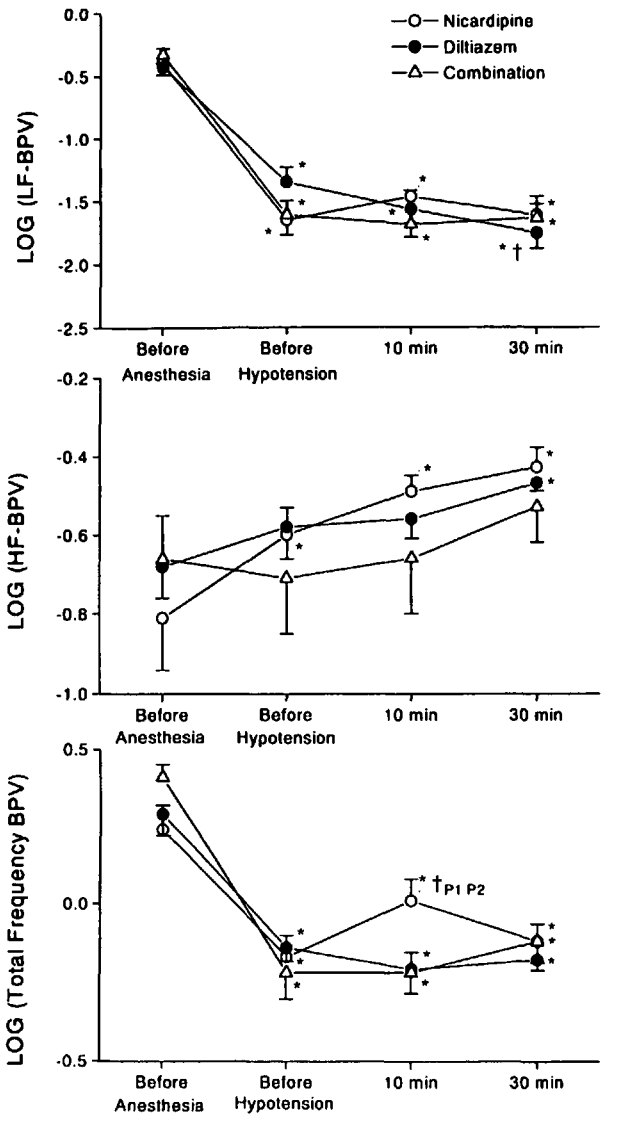

FIGURE 5 Logarithmic change in blood pressure variability (BPV) after administration of nicardipine, diltiazem or combination of nicardipine and diltiazem.
* $P < 0.05$ *vs* Before Anesthesia. † $P < 0.05$ *vs* Before Hypotension.
P1 $P < 0.05$ *vs* Diltiazem. P2 $P < 0.05$ *vs* Combination.
Error bars denote SEM.

be poorly adapted to the technique of induced hypotension.[2] Doses of diltiazem necessary to obtain a decrease in blood pressure might be accompanied by electrophysiological modifications such as atrioventricular conduction impairment.[7] Diltiazem might reduce the dose requirement for nicardipine-induced hypotension, similar to nitroprusside-induced deliberate hypotension.[4] The differences in pharmacological properties between diltiazem and nicardipine suggest that combinations of these drugs may produce a remarkable hypotension synergism and provide a better pharmacological profile than could be provided by any agents used alone and is advocated for induced hypotension.

Spectral analysis of HRV and BPV has been used to estimate sympathetic and parasympathetic activity.[8,9] Japundzic *et al.* showed that LF-HRV arises from both sympathetic and parasympathetic activities, whereas LF-BPV originates exclusively from sympathetic tone in conscious rats.[21] Thus, sympathetically maintained phasic characteristics of vascular tone may play a major role in the genesis of LF-BPV. We expected LF-BPV to be a more sensitive index of sympathetically maintained reflex responses to induced hypotension than was HF-BPV. Contrary to our expectations, the current study shows that LF-BPV in the three study groups was unchanged throughout the period of induced hypotension. The unchanged LF-BPV may be due to the potent vasodilating effects of calcium channel blockers.

We noted a difference in blood loss among the three study groups. Blood loss in hip surgery may be related to many factors. As noted in the Table, there were no differences among the three groups with respect to operative time or percent change of blood pressure. The total amount of blood loss did not differ between surgery for total hip arthroplasty and for rotatory acetabular osteotomy. We speculate that the combined therapy group may be at a clinical advangtage because of the ease of the decrease in blood pressure with less reflex tachycardia than nicardipine alone, resulting in reduced blood loss.

The current study shows that reflex tachycardia to decreased arterial pressure by nicardipine infusion does not develop with loading dose of diltiazem. It is logical that diltiazem limits the sympathetically mediated responses of heart rate and LF-HRV to nicardipine infusion, and potentiates nicardipine induced deliberate hypotension. Thus, a loading dose of diltiazem and continuous infusion of nicardipine in combination may be preferred during calcium channel antagonists induced hypotension.

Concomitant inhalational anesthetic agent and muscle relaxant administration may influence the autonomic nervous control of pulse rate and blood pressure variability by altering central autonomic outflow. Ebert *et al.* demonstrated, by microneurography, that sevoflurane anesthesia was not associated with alteration in sympathetic nervous activity in humans.[22]Thus, we selected sevoflurane/nitrous oxide-anesthesia in the current study. The timing of administration of vecuro-

nium was not controlled, since vecuronium usually does not change heart rate and mean blood pressure compared with other muscle relaxants.[23]

The primary limitation of this study is that analysis of a short epoch of HRV and BPV data provides information only on autonomic modulation of the heart, and not on functioning autonomic nerve activities. Because of technical difficulties and risks, cardiac autonomic outflow has not been directly measured in humans, and we could not compare HRV and BPV with actual cardiac autonomic nerve activities. Thus, the exact mechanism of the increase in LF-HRV in the nicardipine group could not be identified with the methods used in this study.

In conclusion, HRV and BPV analysis demonstrated that the use of diltiazem and nicardipinein combination for acute, induced hypotension proved to be better for attenuating reflex response of symapathetic activation to induced hypotension.

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