

Research Article

General Anesthesia in Hypertensive Patients: Impact of Pulse Pressure but not Cardiac Diastolic Dysfunction on Intraoperative Hemodynamic Instability

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Abstract

In hypertensive patients undergoing general anesthesia, elevated pulse pressure (PP) (>60 mmHg) and/or diastolic dysfunction (DD) could be risk factors for intraoperative hemodynamic instability. The aim of this observational study was to investigate the contribution of DD and preoperative PP with the occurrence of intraoperative hemodynamic instability. Hypertensive (n=61) and normotensive (n=21) patients were scheduled to undergo urologic surgery under general anesthesia. DD was graded according to preoperative Doppler echocardiography, and preoperative brachial PP was calculated during anesthetic consultation. Episodes of hypertension and hypotension were recorded during the intraoperative period. For statistical analysis, hypertensive patients were divided into groups according to the presence or not of DD. The relationship between PP and hemodynamic instability index was assessed using multiple regression analysis. Sixty-three percent of hypertensive subjects had a PP > 60 mmHg. Among hypertensives, 30 (49%) had no DD, 19 (31%) had a mild DD and 12 (20%) had a moderate or severe DD. By comparison with controls, hemodynamic instability undex. This index was positively correlated with PP, even after adjustment on age, body mass index and mean arterial pressure (r = 0.56; p < 0.0001). The study provides evidence that increased intraoperative hemodynamic instability during general anesthesia in urologic hypertensive subjects is associated with increased preoperative brachial PP. DD does not contribute to intraoperative hemodynamic instability.

Keywords: Hypertension; Pulse pressure; Cardiac diastolic dysfunction; General anesthesia; Hemodynamic instability

Abbreviations: PP: Pulse Pressure; LV: Left Ventricular; DD: Diastolic Dysfunction

Introduction

Guadeloupe is characterized by one of the higher prevalence of prostate cancer in the world. In French Caribbean regions, 48.3% of women and 55.6% of men above 50 years suffer from hypertension [1]. Thus, urologic surgery is frequently performed on an elderly population with a high prevalence of hypertension. Classically, hypertensive patients tend to be more hemodynamically unstable during general anesthesia than normotensive subjects [2-5]. However, the likelihood of experiencing hemodynamic instability is difficult to predict in this population [3,5,6]. In a recent report [7], preoperative and intraoperative predictors of cardiac adverse events have been studied after general, vascular and urological surgery. The results of this survey have shown that in comparison with current risk stratification and disease, the use of intra operative measurements of mean arterial pressure and heart rate improved markedly the ability to predict perioperative event [7].

A study of hemodynamic instability during general anesthesia is important to determine the associated risk factors. Schematically, hemodynamic instability is influenced by both cardiac and vascular factors. First, in subjects with preserved ejection fraction, left ventricular (LV) diastolic dysfunction (DD) might be one of the major determinants of cardio vascular events [8-11]. However, a possible relationship between LVDD and intraoperative hemodynamic instability has never been studied. Second, pulse pressure (PP) has been widely studied and confirmed as a cardiovascular risk marker [12]. Thus, increased PP is the most independent predictor of cardiovascular risk in old subjects with hypertension [13,14]. Moreover, PP was associated with adverse postoperative outcome [15,16]. Therefore, our working hypothesis is that DD and preoperative PP could be risk factors of intraoperative hemodynamic instability.

The aim of this study was to investigate, during general anesthesia, the contribution of DD and/or preoperative PP with the occurrence of hemodynamic instability during urologic surgery, which were brought about by induction of anesthesia or by the operative procedure itself.

Patients and Methods

This observational study was approved by the Comité de Protection des Personnes Sud-Ouest et Outre Mer III (N° 2007-A00815-48) on 25 July 2007 and written informed consent was obtained from the patient. All data used in subsequent analyses were anonymized.

Patients

All patients scheduled for an urologic intervention and addressed to

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the anesthetic consultation were screened to be prospectively enrolled in the study. Baseline characteristics included: age; body mass index (BMI); body surface area; sex; American Society of Anesthesiologists (ASA) class; diabetes; and brachial preoperative PP obtained during anesthetic consultation. Data related to operative procedures included type of surgical procedures, total dose of ephedrine prescribed, estimated blood loss and intraoperative volume replacement; anesthesia and operative times.

Inclusion criteria: Patients were classified as hypertensive if they had a history of hypertension confirmed by their general practitioner or cardiologist. Patients unaware of their hypertension status, but with a systolic blood pressure (SBP) > 180 mmHg during the anesthetic consultation were considered hypertensive and addressed for subsequent evaluation. Patients with isolated hypertension during anesthetic consultation ("white-coat hypertension") were classified as indeterminate regarding hypertension status.

Exclusion criteria: Patients scheduled for regional anesthesia, renal transplantation, surgery for pheochromocytoma or Conn adenoma, were not included in the study. Exclusion criteria also included history of congestive heart failure or known LV ejection fraction < 40%, idiopathic hypertrophic cardiomyopathy, arrhythmia, significant heart valve disease, sickle cell disease and age < 18 years. Patients classified as indeterminate regarding hypertension status were also excluded.

Control patients: In order to confirm that hypertensive patients suffered more from hemodynamic instability and that they had different echocardiographic results, we have also included normotensive patients. Patients were classified as normotensive if they had no history of hypertension and their blood pressure values during the anesthetic consultation were < 140 mmHg for systolic and < 90 mmHg for diastolic pressures.

Methods

Anesthetic management and intraoperative care

Premedication was given orally 2h before induction of anesthesia and consisted of hydroxyzine for all patients. Cardiovascular drugs were taken with the premedication except for angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors.

General anesthesia was induced with propofol 2.5 mg kg⁻¹ and sufentanil 0.25 g kg⁻¹. After orotracheal intubation facilitated by cisatracurium 0.15 mg kg⁻¹, anesthesia was maintained with 0.7-1.5% end-tidal sevoflurane. Train of four monitoring was used to assess the depth of paralysis and adjust cisatracurium delivery. Reversal of neuromuscular blockade was performed when indicated. Crystalloids were infused during operation at a basal rate of 10 ml kg⁻¹ h⁻¹. Inspired oxygen fraction was set at 50% in air or nitrous oxide and minute ventilation adjusted to maintain end-tidal CO₂ below 40. Boluses of ephedrine 3 or 6 mg and additional iv fluids were administered according to changes in arterial pressure.

Surveillance of hemodynamic parameters (heart rate and blood pressure) was performed by one of the anaesthesiologists involved in the study. Blood pressure was measured by an automatic oscillotonometric arm cuff device every 5 min (HP Viridia[™]; Aligent technologies Andover MA). During induction of anesthesia, hemodynamic parameters were systematically recorded during 3 time points: 1) baseline before general anesthesia (BL-GA); 2) just before tracheal intubation (POST-IND); 3) just after tracheal intubation (POST-INT). Therapeutic interventions included administration of ephedrine,

additional i.v fluids, and use of antihypertensive drugs. Modifications of sevoflurane delivery and administration of sufentanil only for the purpose of blood pressure control were also considered as therapeutic interventions. Therapeutic interventions were quantified by the use of a therapeutic index defined as follow. Therapeutic index: 1 - [(number of hypotensive and hypertensive episodes - number of therapeutic intervention) / number of hypotensive and hypertensive episodes].

Definitions of Intraoperative Hemodynamic Events

Hemodynamic instability

Hypotension: defined as a SBP less than 80% of baseline [17] or less than 70% for baseline SBP above 180 mmHg. A minimum interval of 20 min was taken into account to consider a new episode of hypotension, except when a therapeutic intervention was performed or SBP returned to value above 80% or 70% of baseline. Baseline was defined as the arterial pressure values before induction of general anesthesia [17].

Hypertension: defined as a SBP > 160 mmHg. A minimum interval of 20 min was taken into account to consider a new episode of hypertension, except when a therapeutic intervention was performed or SBP returned to value less than 160 mmHg.

Hemodynamic instability index: The sum of hypertensive and hypotensive episodes during intraoperative period. In order to take into account the different anesthesia durations, the number of hypotensive or hypertensive episodes was divided by the duration of anesthesia in min. Hemodynamic instability index was expressed as the number of hypertensive and hypotensive episodes x 20 min⁻¹, because a minimum interval of 20 min was taken into account to consider a new episode of hypertension or hypotension.

Bradycardia

Heart rate (HR) < 45 bpm for at least 1 min. A minimum interval of 20 min was taken into account to consider a new episodes of bradycardia, except when a therapeutic intervention was performed or HR returned to value > 45 bpm.

Tachycardia

Heart rate > 100 bpm for at least 1 min. A minimum interval of 20 min was taken into account to consider a new episode of tachycardia, except when a therapeutic intervention was performed or HR returned to value < 100 bpm.

Protol Study

Brachial pulse pressure

Brachial pulse pressure is the difference between systolic and diastolic pressure. A PP > 60 mmHg was considered to identify patients with increased cardiovascular mortality [14].

Doppler echocardiography

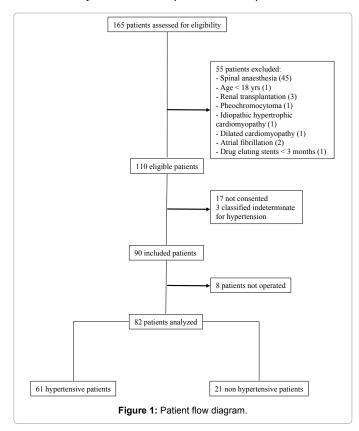
Preoperative assessment of DD was performed in awake patients during the two weeks following anesthetic consultation. Transthoracic Doppler echocardiography was performed with the use of a HDI 5000 imaging system model (ATL ultrasound, Bothell, WA, USA). The LV ejection fraction was assessed using the biplanar Simpson method. Left ventricular mass (LVM) was calculated from M-mode according to the Penn convention method: LVM (g) = 1.04 [(septum + posterior wall + LV internal diastolic dimension)³ - (LV diastolic dimension)³] - 13.6 g. Left ventricular mass was normalized for height to the power of 2.7.

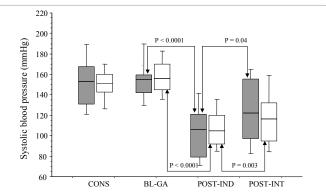
Diastolic function was assessed in all patients using pulsed Doppler peak E and A velocities, E/A ratio [8-10]. Tissue Doppler imaging (TDI) of the mitral annulus was obtained from the apical 4-chamber view [18]. The peak Ea velocity was used to calculate a lateral E/Ea ratio. DD was graded as normal, mild, moderate or severe dysfunction according to the criteria described below [9,19]. Normal diastolic function required an 0.75 < E/A <1.5 and an E/Ea < 10. Mild DD was defined as an E/A \leq 0.75 and an E/Ea < 10. Moderate DD was defined as a 0.75 < E/A <1.5 and an E/A ratio of \leq 0.75 and an E/Ea > 10 [19]. Severe DD was defined as an E/A \geq 1.5.and an E/Ea \geq 10.

Recordings were stored on a videotape recorder. Videotapes were reviewed on an off-line analyzer system that allowed slow-down or stop of the picture. Sixteen randomly selected Doppler echocardiography recordings were used to assess interobserver and intraobserver variability in the measurement of posterior wall thickness and peak Ea velocity.

Statistical analysis

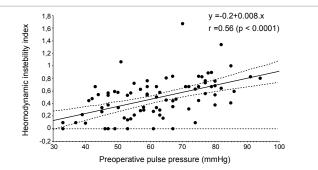
Data were computerized and analyzed using Statview 5.0 statistical packages (SAS Institute Inc., Cary, USA). Normality of the distribution of data was assessed by the Kolmogorov-Smirnov test. We expressed continuous variables as the mean \pm SD or as the median [25th – 75th percentiles] when appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test, and continuous variables were compared using the Student's t test or Mann-Whitney U test when appropriate. Hypertensive patients were divided into 2 groups according to the presence or not of a DD (normal diastolic function vs mild, moderate and severe DD). Changes in arterial pressure during anesthesia induction were analyzed using repeated measures analyze of variance (ANOVA) followed by the Scheffe F test, as appropriate. The relationship between hemodynamic instability index and PP was

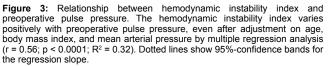




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Figure 2: Course of systolic blood pressure for hypertensive patients with and without diastolic dysfunction during the phase of induction of anesthesia Grey boxes = hypertensive patients with diastolic dysfunction; white boxes = hypertensive patients without diastolic dysfunction; CONS = day of anesthetic consultation; BL-GA = baseline before general anesthesia; POST-IND = just before tracheal intubation; POST-INT = just after tracheal intubation. Data are presented as median, 10^{h} , 25^{h} , 75^{h} , and 90^{h} percentiles. Arrows displayed significant difference within group between different events. The same figure was obtained with brachial pulse pressure.





evaluated by a single linear regression analysis and adjusted on age, BMI, and mean arterial pressure by multiple regression analysis. All comparisons between controls and hypertensive patients were adjusted on age and BMI. A p value < 0.05 was considered significant.

Preliminary results showed that the frequency of hypotensive or hypertensive episodes in hypertensive patients during anesthesia was around 60%, which was in accordance with previous studies [17,20]. On the basis of a relevant 30% change in frequency in hypotensive and hypertensive episodes between hypertensive patients with and without DD, 29 patients should be included in each groups to achieve a power of 80% and for a two-sided type I error of 0.05.

Results

Sixty-one hypertensive patients were included (Figure 1). Patients had a duration of hypertension less than 5 years for 46% of them, between 5 to 20 years for 36% and more than 20 years for 18%. Patients took a median of 2 antihypertensive drugs, and 21% were treated with 3 or more drugs. Angiotensin-receptor antagonists were prescribed for 49% of patients followed by diuretics (41%), calcium-channel antagonists (39%), ACE inhibitors (25%), and beta-blockers (25%).

Doppler echocardiography was performed in all hypertensive patients and in 21 controls. Interobserver variability in the measurement

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Variables	Patients without diastolic dysfunction (n = 30)	Patients with diastolic dysfunction(n = 31)	P value	All hypertensive patients (n = 61)	Controls (n = 21)	P value
Age (yr)	65 ± 10	66 ± 8	0.74	66 ± 9	58 ± 12	0.003
Sex male (n; %)	28 (93)	30 (97)	0.53	58 (95)	18 (86)	0.18
Body mass index (kg.m ⁻²)	26.5 ± 3.6	26.3 ± 3.7	0.84	26.4 ± 3.6	24.4 ± 3.2	0.03
ASA score (n, %)						
- class 1	-	-	0.47	-	11 (52)	0.0004
-class 2	25 (83)	28 (90)	0.47	53 (87)	10 (48)	0.0001
- class 3	5 (17)	3 (10)		8 (13)	0	
Diabetes (n, %)	8 (27)	10 (32)	0.78	18 (29)	4 (19)	0.34
Preoperative pulse pressure (mmHg)	67 ± 14	63 ± 13	0.31	65 ± 13	53 ± 13	0.03
Preoperative pulse pressure > 60						
mmHg	21 (70)	17 (55)	0.22	38 (63)	6 (29)	0.008
(n, %)				. ,		
Surgical procedures (n, %)						
- radical prostatectomy	14 (47)	16 (52)		30 (49)	10 (48)	0.07
- transurethtral procedures	6 (20)	6 (19)	0.40	12 (20)	3 (14)	0.37
- laparoscopic lymph node removal	4 (13)	7 (23)		11 (18)	1 (5)	
- miscellaneous	6 (20)	2 (6)		8 (13)	7 (33)	
General anesthesia						
 propofol (induction; mg.kg⁻¹) 	2.4 ± 0.62	2.8 ± 1.2	0.15	2.6 ± 1.0	3.0 ± 0.7	0.07
- sufentanil (induction; µg.kg ⁻¹)	0.24 ± 0.06	0.23 ± 0.08	0.51	0.23 ± 0.07	0.25 ± 0.07	0.35
- cisatracurium (n, %)	19 (63)	23 (74)	0.36	23 (74)	14 (67)	0.99
- minimum alveolar concentration of	1.2 ± 0.93	1.2 ± .37	0.81	1.2 ± 0.7	1.3 ± 0.9	0.48
sevoflurane (%)						
- sufentanil (total dose, µg.kg ⁻¹)	0.66 ± 0.44	0.57 ± 0.33	0.37	0.60 ± 0.4	0.59 ± 0.3	0.83
Ephedrine (total dose, mg)	6 [0 – 15]	6 [0 - 9]	0.69	6 [0 – 12]	6 [0 - 9]	0.27
Estimated blood loss (ml)	200 [0 -713]	200 [0 - 500]	0.98	200 [0 - 500]	325 [0 - 425]	0.97
Intraoperative volume replacement (ml)		1500 [812 – 2000]	0.65	1500 [1000 – 2000]	2000 [950 - 2125]	
Median anesthesia time (min)	190 [115 – 220]	165 [109 – 218]	0.56	175 [112 – 220]	185 [112 - 240]	0.74

Table 1: Characteristics of hypertensive patients and controls.

	Hypertensive patients without	Hypertensive patients with	P Value	All hypertensive patients	Controls	P value
	diastolic dysfunction (n = 30)	diastolic dysfunction (n = 31)		(n = 61)	(n = 21)	
Episodes of hypotension (n.20 min ⁻¹)	0.53 ± 0.30	0.53 ± 0.33	0.55	0.53 ± 0.31	0.31 ± 0.23	0.04
Episodes of hypertension (n.20 min ⁻¹)*	0.01 ± 0.06	0.00 ± 0.02	0.59	0.01 ± 0.05	0.01 ± 0.03	0.89
Hemodynamic instability index	0.55 ± 0.30	0.54 ± 0.33	0.93	0.57 ± 0.33	0.32 ± 0.24	0.04
Therapeutic index	0.54 [0.33 - 1.0]	0.75 [0.25 - 1.0]	0.85	0.67 [0.33 - 1.00]	1.00 [0.69 - 1.00]	0.01
Patients with bradycardia, n (%)	10 (33)	10 (32)	0.99	20 (33)	3 (14)	0.16
Patients with tachycardia, n (%)	2 (7)	2 (6)	0.99	4 (7)	1 (5)	0.99

*: 6 patients without diastolic dysfunction and 3 patients with diastolic dysfunction experienced hypertension episode

Table 2: Intraoperative hemodynamic instability according to the presence of diastolic dysfunction in hypertensive patients and controls.

of posterior wall thickness and peak Ea velocity were 7.6 \pm 2.2% and 3.2 \pm 1.6%, respectively, with intraobserver variability of 6.5 \pm 1.9% and $2.7 \pm 1.4\%$, respectively. All controls had a normal echocardiographic diastolic function. Among the 61 hypertensive patients, 30 (49%) had a normal diastolic function, 19 (31%) had a mild DD and 12 (20%) had a moderate or severe DD. Ejection fraction was similar between hypertensive patients with and without DD (64 \pm 8 vs. 67 \pm 8 %; p = 0.14). No difference was found between hypertensive patients and controls (65 \pm 8 vs. 66 \pm 8 %; p = 0.84). Left ventricular mass index was similar between hypertensive patients with and without DD (44.8 \pm 11.3 vs. 44.0 \pm 12.1 g.m^{-2.7}; p = 0.29). Left ventricular mass index tended to be different between hypertensive patients and controls (42.4 \pm 11.7 vs. 36.2 \pm 9.0 g.m^{-2.7}; p = 0.07). Treatment of hypertension did not differ between the different DD groups. There was no relation between the duration of hypertension and the severity of DD. The clinical characteristics of the patients are summarized in (Table 1).

Intraoperative hemodynamic changes

After induction of general anesthesia, hypertensive patients and controls experienced a significant SBP fall, but after orotracheal intubation, only hypertensive patients had a significant increase in SBP (data not shown). Course of SBP during induction of general anesthesia between hypertensive patients with and without DD are depicted in (Figure 2) The presence of a DD did not influence the course of SBP and the magnitude of change of SBP. The same feature was observed with brachial PP.

During intraoperative period, hypertensive patients suffered

from more hemodynamic instability compared to controls, even after adjustment by age and BMI (Table 2). Hemodynamic instability index was not statistically different between patients with and without DD. Preoperative PP was different between hypertensive patients and controls (even after adjustment by age and BMI), but not between patients with and without DD (Table 1).

Hemodynamic instability index varies positively with preoperative PP, even after adjustment on age, BMI, and mean arterial pressure by multiple regression analysis (r = 0.56; p < 0.0001; R² = 0.32) (Figure 3). Hemodynamic instability index varies positively with SBP (r = 0.45; p < 0.0001), but no relationship could be found with diastolic arterial pressure (r = 0.15; p = 0.18).

Discussion

In the present study, we confirmed that hypertensive subjects during general anesthesia suffered more from hemodynamic instability than controls. Interestingly, the presence of a DD had no significant impact on hemodynamic instability, but a positive relationship between this variable and preoperative brachial PP was found.

This study has potential limitations. First, it was performed at a single medical center and deserves further confirmation in other institutions. Second, therapeutic interventions were not standardized. However, only 3 anaesthesiologists were involved which limited heterogeneous treatment. Third, a relationship between intraoperative hemodynamic instability and postoperative cardiovascular complications could not be demonstrated with the number of patients included. Although hypertension is a major risk factor for cardiovascular disease, its impact

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during the perioperative period is less clear [3,5,21]. In hypertensive patients, the likelihood of experiencing an adverse perioperative cardiac event is low, around 1.3 [3,5].

As previously reported [3-5,20,21], we confirmed that hypertensive patients presented an increased hemodynamic instability during intraoperative period. In our study, episodes of hypotension occurred frequently [2-7,17,20,21] and could be more detrimental than hypertension episodes [2-4,6,7,20]. However, since therapeutic interventions were less frequent in hypertensive subjects, physicians have probably considered that the attained level of blood pressure could not influence consistently the outcome [22]. Main problem related to hemodynamic instability remains loading conditions. We cannot provide direct measurement of filling pressures. However, blood losses and intraoperative volume replacement are similar in the different groups.

In the complications related to hypertension, DD recently received particular attention [8,9]. In the community, 52.7% of hypertensive patients had a normal diastolic function, 34.5% had a mild DD, and 12.8% a moderate to severe DD [9]. Likewise, in a population \geq 65 year of age, more than 60% had diastolic filling abnormalities in a preoperative setting [23]. Our proportions of diastolic filling abnormalities were quite close to these studies.

DD is characterized by increased left ventricular chamber stiffness [10,24]. As a result, chamber compliance is reduced, the time course of filling is altered, and the diastolic pressure is elevated [8,24]. During the perioperative period, hemodynamic changes and anesthetic agents could adversely affect LV diastolic function [11] and could jeopardize the hemodynamic stability. We were unable to demonstrate that DD played a major role in intraoperative hemodynamic instability during urologic surgery. Several points should be addressed to. First, for definition of DD echocardiographic we took into account parameters well recognized and easy to obtain [9,10] and we refered to a classification used in recent studies and reviews [9,10,18,19]. Second, the impact of DD could have been easier to show in other type of surgery like aortic and major vascular surgery, in which the magnitude of hemodynamic changes could be more important. Third, using echocardiography, Filipovic et al [25] found that sevoflurane did not influence LV relaxation, and that propofol caused only small impairment [25]. Lastly, all patients were intraoperatively treated with relative fluid restriction (basal rate below 10ml.kg⁻¹.L⁻¹) [26], prone to avoid fluid overload.

Our study suggested that patients with wide preoperative PP are predisposed to hemodynamic instability. Pulse pressure arises from the interaction of cardiac ejection (stroke volume) and the properties of the arterial circulation. This parameter is a predictor of cardiovascular risk when it is above 60 mmHg [14]. In our study, 60% of hypertensive patients have a preoperative PP > 60 mmHg, underlying the clinical severity of their hypertension. At a given stroke volume, arterial stiffness and wave reflections are the main determinants of increased PP [12]. Endothelial dysfunction and inflammatory factors may also contribute [27]. In anesthesia practice, it might be useful to consider PP as an important and new clinical predictor for hemodynamic instability. Such hemodynamic events may indeed contribute to serious morbidity over the entire perioperative period [5-7,20,28]. This is particularly true in elderly hypertensive population were changes in normal auto-regulatory process have frequently disappeared [22]. As PP was associated with an increased incidence of postoperative cardiovascular complications [15,16], future research on a relationship between PP, hemodynamic instability and cardiovascular complications could be interesting to promote.

Other pathophysiological mechanisms could be also involved to explain the increased hemodynamic instability in hypertensive patients. Hypertensive patients aged ≥ 65 years tended to have both an increase in systemic sympathetic nervous system activation and an increase in vascular alpha-adrenergic responsiveness [29]. Hypertension is also accompanied by an impairment of the baroreflex mechanisms [30]. Moreover, the recovery profiles of baroreflex are probably different between hypertensive and normal individuals [31]. Lastly, the effects of anesthesia are even more pronounced in hypertensive patients, which place them at risk of profound hypotension [32]. As expected from cerebral auto regulatory mechanisms, the organism defense against blood pressure rise was superior to that of corresponding fall. On the other hand, stimuli that enhanced vascular adrenergic responsiveness might contribute to paroxystic hypertension [33].

In conclusion, increased hemodynamic instability during general anesthesia in urologic hypertensive subjects can be predicted by preoperative brachial PP. DD does not contribute to intraoperative instability.

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