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ORIGINAL ARTICLE

Comparison of epinephrine and felypressin pressure effects in 1K1C hypertensive rats treated or not with atenolol

Camila A. Fleury · Vagner C. Andreo · Pedro C. Lomba · Thiago J. Dionísio · Sandra L. Amaral · Carlos F. Santos · Flávio A. Faria

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Abstract
Purpose Epinephrine is considered the gold standard vasoconstrictor for hypertensive patients, but few studies report felypressin's effects. The present study aimed to analyze and compare the effects of these two vasoconstrictors, injected by the intravenous route, on the arterial pressure of normotensive, hypertensive and atenolol-treated hypertensive rats.
Method The hypertension model was one-kidney-one-clip (1K1C): the main left renal artery was partially constricted and the right kidney was surgically removed in 45-day-old male Wistar rats. 1K1C hypertensive rats received atenolol (90 mg/kg/day) by gavage for 2 weeks. 28–35 days after hypertension induction, a catheter was inserted into the left carotid artery to record direct blood pressure values. The following parameters were recorded: minimal hypotensive response, maximal hypertensive response, response duration and heart rate.
Results Epinephrine, but not felypressin, exerted an important hypotensive action; non-treated hypertensive rats showed more pronounced vasodilation. Treated and non-treated rats showed hypertensive responses of the same magnitudes in all groups; 1K1C atenolol rats showed reduced hypertensive responses to both vasoconstrictors. Felypressin's response duration was longer than that of epinephrine in all groups. Epinephrine increased heart rate while felypressin reduced this parameter only in the normotensive group.
Conclusions Our results suggest that felypressin has equipotent pressure responses when compared with epinephrine, showing a greater extent of action. Atenolol's reduction of hypertensive effects surprisingly suggests that atenolol β-blockade may also be important for felypressin's cardiovascular effect, as is widely known for epinephrine. Our data suggest that felypressin is safe for hypertensive subjects, in particular those receiving atenolol.

Keywords Felypressin · Epinephrine · 1K1C hypertension · Atenolol · Vasoconstrictors

Introduction

Vasoconstrictor drugs are normally added to local anesthetics to provide long-term anesthesia. The expected action of such molecules is to increase anesthetic safety and duration by diminishing absorption to blood vessels, and improve surgery outcomes by reducing bleeding. Despite these expected effects, there are studies showing vasoconstrictor absorption after local injection of anesthetic cartridge [1]. Since most vasoconstrictor drugs, such as epinephrine, are sympathetic nervous system agonists, systemic effects may include vasoconstriction, vasodilation of skeletal muscle beds and cardiac positive chronotropic and inotropic effects. Felypressin (octapressin) has a

C. A. Fleury · V. C. Andreo · T. J. Dionísio · C. F. Santos (✉) · F. A. Faria
Department of Biological Sciences, Bauru School of Dentistry, University of São Paulo, Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP 17012-901, Brazil
e-mail: cebola@usp.br

P. C. Lomba
Dentsply Pharmaceutical, Rua Igarapava, 436, Catanduva, SP 15810-255, Brazil

S. L. Amaral
Department of Physical Education, School of Science, São Paulo State University, Av. Eng. Luiz Edmundo Carrijo Coube, 14-01, Bauru, SP 17033-360, Brazil

distinct action since, being a synthetic vasopressin analog, it binds specifically to V_1 receptors, and thus does not show any interaction with sympathetic receptors [2].

The American Dental Association reports that epinephrine is the safest vasoconstrictor drug for cardiovascular patients, notably hypertensives, using a 56-μg dose as the maximum limit, which is present in three local anesthetic cartridges containing epinephrine at 1:100,000 concentration [3]. Epinephrine is the vasoconstrictor of choice in hypertensive patients due to vasodilation by interaction with β_2-adrenoceptors that may offset other increasing blood pressure effects. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [4], hypertensive patients, controlled or not, who present with up to 160–100 mmHg can undergo dental treatment and epinephrine is not contraindicated (but do not use more than 54 μg of epinephrine contained in three cartridges with 1:100,000 concentration) [5].

Scant information is available on felypressin use in patients with cardiovascular disease. A study in patients who suffered acute myocardial infarction in the last six months or unstable angina pectoris showed no intra-surgical complications in 79 dental extractions or pulpectomies using 1–2 prilocaine–felypressin anesthetic cartridges [6]. Fewer hemodynamic effects in cardiac-transplanted patients were observed when felypressin was applied as compared with epinephrine [7].

The aim of this study was to evaluate and compare the effects of direct intravenous injection of epinephrine and felypressin on blood pressure of normotensive, hypertensive and atenolol-treated hypertensive rats. The hypertension model adopted was the one-kidney-one-clip (1K1C), described by Goldblatt, since its development is similar to human essential hypertension. Atenolol was chosen because it is one of the most used medications to treat essential hypertension [8].

Materials and methods

Animals and experimental hypertension method

Male Wistar rats weighing 140–320 g provided by Bauru School of Dentistry facilities were used in all groups of this study. The study was approved by the institutional review board before experiments (protocol #029/2007).

All rats received normal diet, free water and food access and were exposed to a 12-h light/dark cycle. Forty five-day-old rats weighing 140–180 g were anesthetized with an injection of ketamine (50 mg/kg of body weight; Dopalen®, Sespo Industry and Trade Ltda., Animal Health Vetbrands Division, Jacareí, São Paulo, Brazil) plus xylazine hydrochloride (10 mg/kg of body weight; Anasedan®, Sespo) and had their abdomen opened to expose the left kidney. After renal artery isolation, a 0.25-mm gap silver clip was installed around this artery, then the right kidney was completely removed, and the abdominal cavity sutured. All rats received 0.1 ml (40,000 IU) of small animal antibiotic (Fontoura Wyeth S.A., São Bernardo do Campo, São Paulo, Brazil) at the end of the surgery. The control group was from the same lot and weight but animals did not undergo surgical intervention because we previously reported that rats that underwent only unilateral nephrectomy presented the same blood pressure and vascular activities as intact ones [9].

Indirect and direct blood pressure measurements

1K1C rats were heated in a box with a 100-W lamp for indirect measurement of arterial pressure. Tail pneumatic cuffs were installed and connected to a digital system for indirect blood pressure recording (Physiological Pressure Transducer, AD Instruments Pty. Ltd., Dunedin, Otago, New Zealand). Rats that presented mean arterial pressure equal to or higher than 150 mmHg in indirect measurement 15 days after clip surgery were treated with atenolol (90 mg/kg/day; Cristália Pharmaceutical and Chemical Products, Itapira, São Paulo, Brazil) administered by gavage in 1 ml volume for 2 weeks [8].

All groups had their direct blood pressure measured 28–35 days after clip surgery, or an equivalent time in the control group; after anesthesia with ketamine/xylazine (50/10 mg/kg body weight), a saline-filled polyethylene catheter PE-50 (Clay Adams–Franklin Lakes, New Jersey, USA) with the external extremity occluded was implanted in the left carotid artery. A similar catheter was also inserted into the right jugular vein for intravenous injection during the experiment. The arterial catheter was connected to a pressure transducer coupled to a blood pressure invasive recording system, using appropriate software (physiological pressure transducer; PowerLab 4/30; Chart Pro, AD Instruments Pty. Ltd). The threshold pressure for the hypertensive 1K1C group was 150 mmHg of mean arterial pressure. Experiments on intravenous injection of vasoconstrictor drugs were performed with anesthetized rats immediately after catheter implantation.

Dose–response curves to epinephrine and felypressin

Exogenous epinephrine (Adren®, Hipolabor Farmacêutica Ltda, Belo Horizonte, Minas Gerais, Brazil) diluted in saline was injected in doses of 80, 160, 320, 640 and 1,280 ng in bolus through the vein catheter to obtain dose–response curves. Felypressin (Dentsply Pharmaceutical, Catanduva, São Paulo, Brazil) was used in 0.5, 1, 2, 3 and

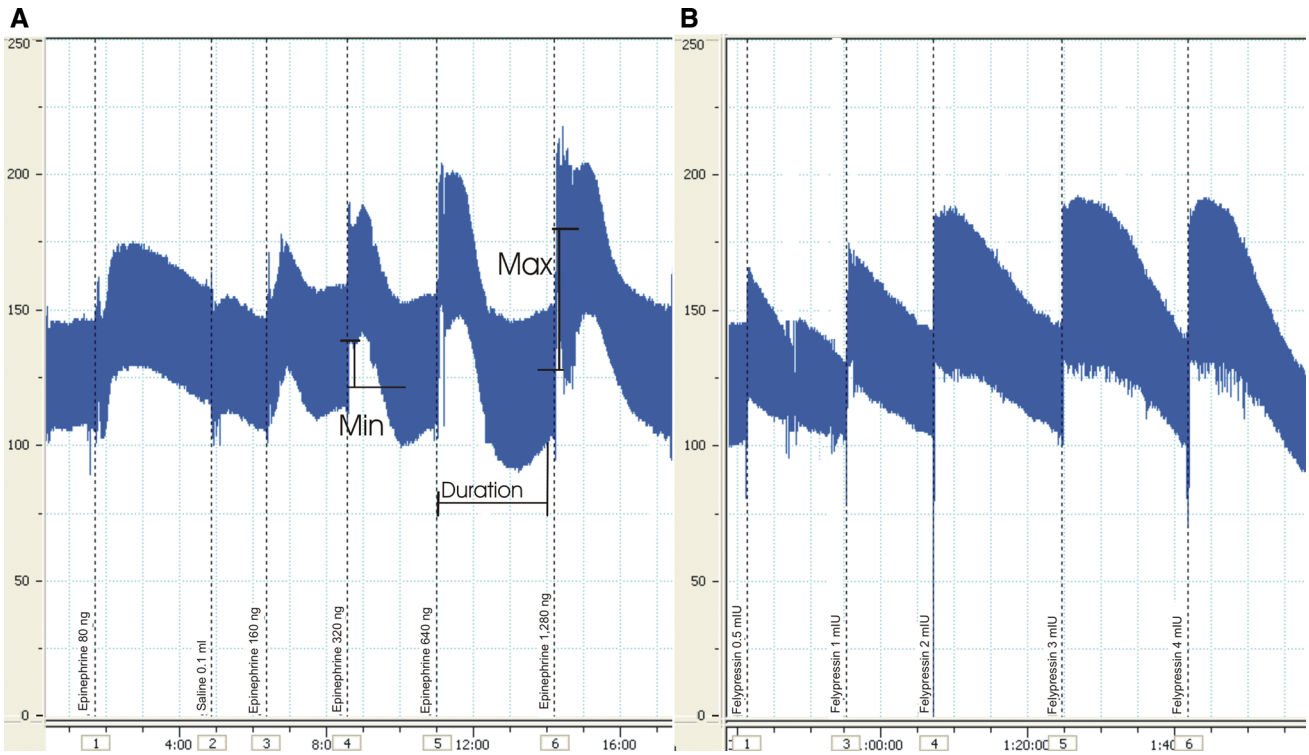

Fig. 1 Typical recording of blood pressure measurements after intravenous in bolus injection of epinephrine (**a**) or felypressin (**b**) in a normotensive rat. *Min* minimal hypotensive response, *Max* maximal hypertensive response, *Duration* response duration

4 mIU. Intravenous injections in random order were performed after a 3-min interval for each response to stabilize blood pressure. Animals were killed with intravenous injection of excess doses of the anesthetic drug thiopental (Thiopentax®, Cristália Pharmaceutical and Chemical Products).

Based on mean arterial pressure (MAP = 1/3 systolic pressure + 2/3 diastolic pressure), the following parameters were analyzed: minimal hypotensive response (difference between minimal and basal MAP), maximal hypertensive response (difference between maximal and basal MAP) and response duration (corresponding to the interval between drug injection and blood pressure normalization to basal values). Based on pulsative recording, the heart rate was recorded 30 s after injection for 1 min. The heart rate was recorded during this period to avoid bias from longer duration or large blood pressure changes. Basal heart rate values were measured for 1 min starting at 30 s before the first injection. Similar epinephrine and felypressin doses were compared.

Statistics

When more than one response was obtained from the same animal, repeated-measures one-way analysis of variance (ANOVA) was used. To compare complete curves from two or more groups, repeated-measures two-way ANOVA was used. When there was significant difference between the doses in each curve or in independent groups and normal distribution, the comparison was performed by Holm–Sidak's or Tukey's methods. In cases where normal distribution did not occur, data were analyzed by non-parametric Mann–Whitney and Kruskal–Wallis tests. The level of significance in this study was set at 5 % ($p < 0.05$). All tests were performed in Statistica Software (StatSoft South America).

Results

Parameters analyzed

A typical recording of pulsatile blood pressure is shown in Fig. 1. Epinephrine produced a vasodilator response (Fig. 1a), while felypressin showed minimal hypotensive response close to zero (Fig. 1b).

Basal blood pressure values during the first 5 min are summarized in Table 1 and used as initial reference. Atenolol significantly reduced blood pressure in hypertensive animals, whose values were still significantly higher than in control animals.

Table 1 Basal values for mean, systolic and diastolic arterial pressure as well as heart rate

	Mean BP (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart rate (beats/min)
Epinephrine				
Control normotensive (7)	121.40 ± 7.57	131.68 ± 7.34	108.42 ± 7.42	203.44 ± 10.61
1K1C hypertensive (7)	172.42 ± 4.88[a]	188.08 ± 5.86[a]	157.15 ± 3.99[a]	216.57 ± 8.92
1K1C atenolol-treated (7)	157.14 ± 4.18[a,b]	171.38 ± 4.29[a,b]	143.34 ± 4.92[a,b]	199.03 ± 13.83
Felypressin				
Control normotensive (7)	110.58 ± 4.13	123.06 ± 4.40	96.19 ± 3.86	200.9 ± 11.11
1K1C hypertensive (7)	160.12 ± 2.40[a]	179.28 ± 3.24[a]	141.58 ± 2.69[a]	217.67 ± 11.34
1K1C atenolol-treated (6)	149.81 ± 6.68[a,b]	161.86 ± 6.93[a,b]	136.38 ± 6.57[a,b]	203.86 ± 13.66

Basal values for mean, systolic and diastolic arterial pressure as well as heart rate obtained during the first 5 min for control normotensive, 1K1C hypertensive and 1K1C atenolol-treated groups. Number of animals in *parentheses* (*n*). Mean ± standard error of mean

[a] $p < 0.05$ compared with normotensive group

[b] $p < 0.05$ compared with hypertensive group

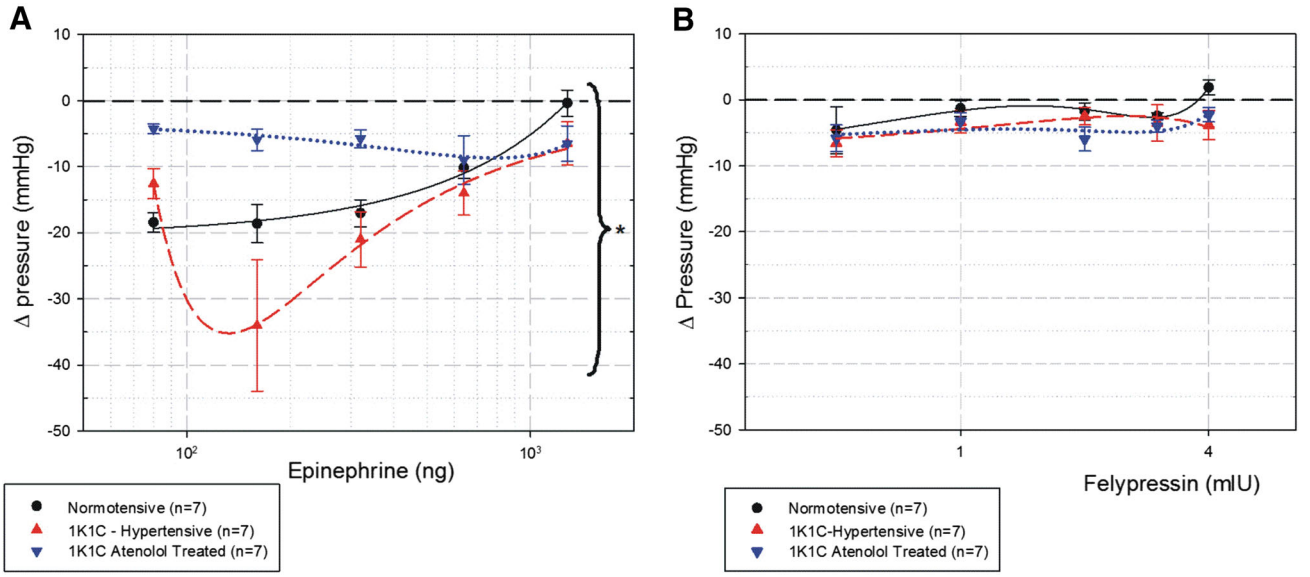

Fig. 2 Minimal hypotensive response curves after intravenous in bolus injection of epinephrine (**a**) or felypressin (**b**) in control normotensive, 1K1C hypertensive and 1K1C atenolol-treated rats. *n* Number of animals. Mean ± standard error of mean. *$p < 0.05$ in the comparison between groups

Minimal hypotensive response

Figure 2 shows epinephrine and felypressin minimal hypotensive response curves. Epinephrine produced greater hypotensive response in lower doses in normotensive and 1K1C non-treated hypertensive groups (Fig. 2a; $p < 0.05$). There was a significant reduction in vasodilator response in the 1K1C atenolol-treated group after epinephrine administration. Felypressin did not show a significant hypotensive response in the three groups studied (Fig. 2b).

Maximal hypertensive response

Maximal hypertensive response curves for epinephrine and felypressin are shown in Fig. 3. Maximal hypertensive responses showed similar increases in blood pressure, which suggests similar potencies for epinephrine (Fig. 3a) and felypressin (Fig. 3b). 1K1C atenolol-treated rats showed significantly lower responses to higher doses of epinephrine and felypressin.

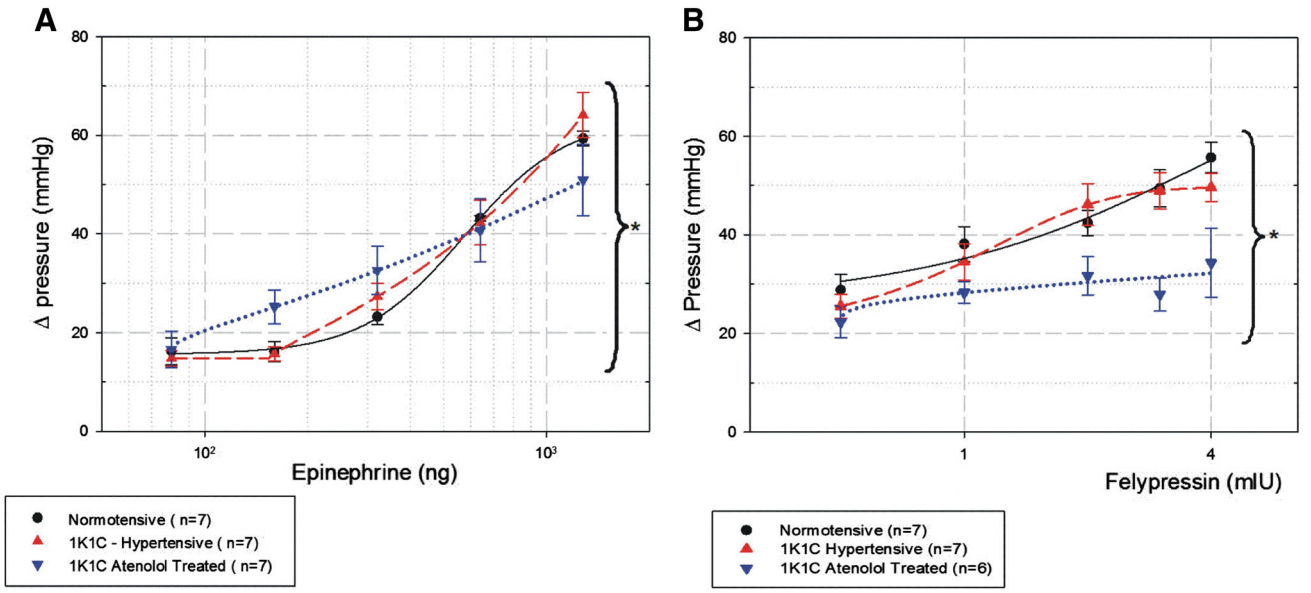

Fig. 3 Maximal hypertensive response curves after intravenous in bolus injection of epinephrine (**a**) or felypressin (**b**) in control normotensive, 1K1C hypertensive and 1K1C atenolol-treated rats. *n* Number of animals. Mean ± standard error of mean. $*p < 0.05$ in the comparison between groups

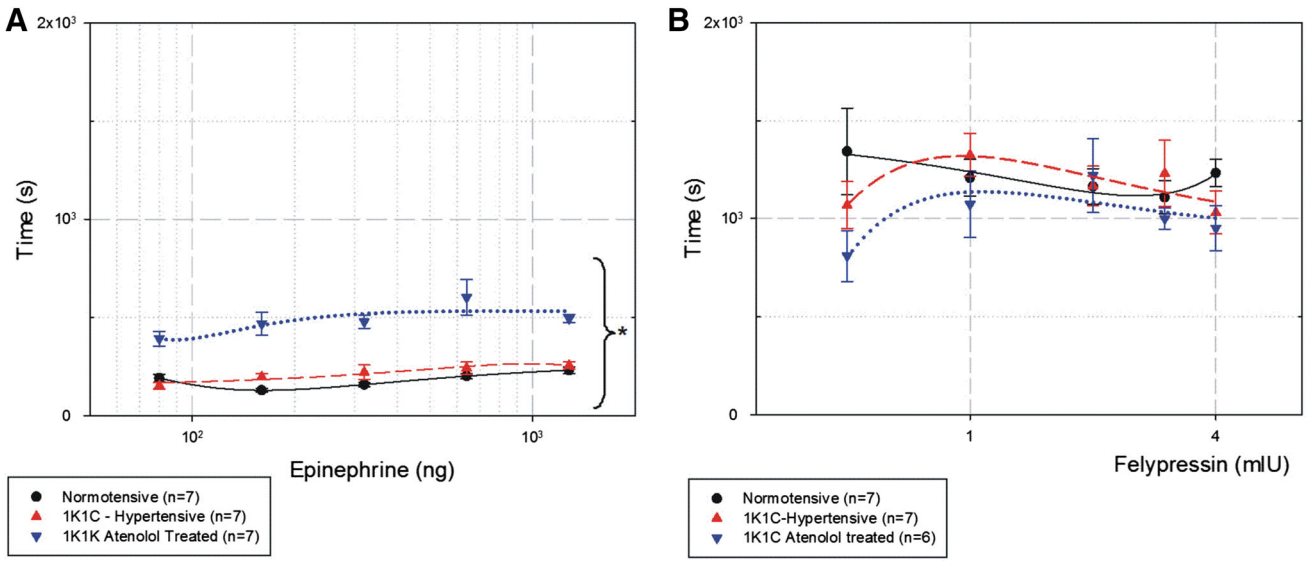

Fig. 4 Response duration after intravenous in bolus injection of epinephrine (**a**) or felypressin (**b**) in control normotensive, 1K1C hypertensive and 1K1C atenolol-treated rats. *n* Number of animals. Mean ± standard error of mean. $*p < 0.05$ in the comparison between groups

Response duration

There was a significant increase in epinephrine response duration for the 1K1C atenolol-treated group (Fig. 4a). Felypressin showed no significant difference in response duration between doses, although all the doses promoted longer responses (approximately 1,200 s; Fig. 4b) when compared with epinephrine (from 220 to 600 s; Fig. 4a).

Heart rate

Epinephrine evoked a significant increase in heart rate for normotensive and 1K1C hypertensive rats, but 1K1C atenolol-treated rats showed no change (Fig. 5a). Felypressin produced a significant reduction in heart rate in normotensive rats, whereas 1K1C hypertensive rats treated or not with atenolol did not show significant alteration.

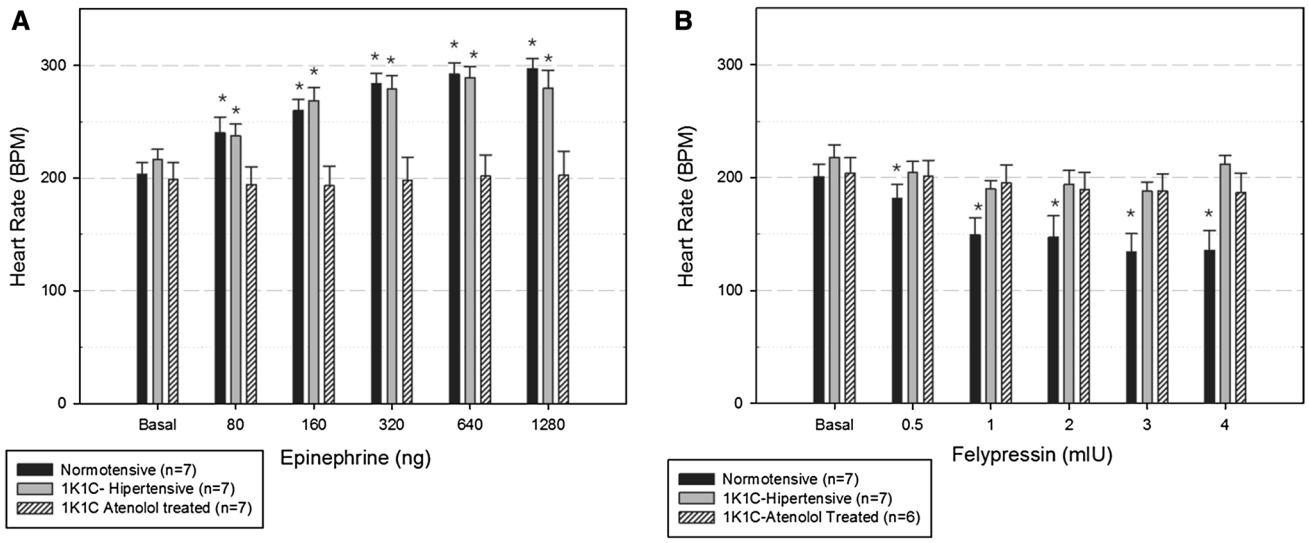

Fig. 5 Heart rate after intravenous in bolus injection of epinephrine (**a**) or felypressin (**b**) in control normotensive, 1K1C hypertensive and 1K1C atenolol-treated rats. *n* Number of animals. Mean ± standard error of mean. *$p < 0.05$ in the comparison to basal values

Table 2 Comparison of epinephrine and felypressin maximal hypertensive response (mmHg)

	Normotensive rats (ΔmmHg)		1K1C hypertensive rats (ΔmmHg)		1K1C atenolol-treated rats (ΔmmHg)	
	Epinephrine (7)	Felypressin (7)	Epinephrine (7)	Felypressin (7)	Epinephrine (7)	Felypressin (6)
Dose 1	16.13 ± 2.03	28.78 ± 3.15*	15.71 ± 1.40	25.51 ± 2.41*	25.23 ± 3.40	22.35 ± 3.20
Dose 2	23.20 ± 1.50	38.10 ± 3.56*	23.20 ± 1.50	34.51 ± 3.69	32.61 ± 4.89	28.25 ± 2.18
Dose 3	43.18 ± 0.54	42.39 ± 2.58	42.28 ± 4.55	46.11 ± 4.27	40.67 ± 6.42	31.67 ± 3.85
Dose 4	59.35 ± 1.48	55.68 ± 3.09	64.11 ± 4.62	49.59 ± 2.80*	50.93 ± 7.29	34.28 ± 6.96

Maximal hypertensive response for similar doses of epinephrine and felypressin in control normotensive, 1K1C hypertensive and 1K1C atenolol-treated groups. *Dose 1* = 160 ng of epinephrine and 0.5 mIU of felypressin; *dose 2* = 320 ng of epinephrine and 1 mIU of felypressin; *dose 3* = 640 ng of epinephrine and 2 mIU of felypressin; *dose 4* = 1,280 ng of epinephrine and 4 mIU of felypressin. Number of animals in *parentheses* (*n*)

* $p < 0.05$ when comparing epinephrine with felypressin at the same dose within the same group

Comparision of epinephrine and felypressin maximal hypertensive response

Epinephrine and felypressin produced no significant difference in the majority of maximal hypertensive responses for the three groups (Table 2).

Discussion

Vasoconstrictor drugs are essential in dental and medical procedures performed under anesthesia, since the local anesthetic must stay in contact with sensitive nerves. It is important to emphasize that in our study no animal died during any of the experiments when the vasoconstrictors epinephrine or felypressin were administered without the local anesthetic agents. It is noteworthy that no deaths were seen even for hypertensive animals that showed a 60-mmHg increase in basal systolic blood pressure. In contrast, other studies have shown that local anesthetics (such as lidocaine and bupivacaine) injected even in low doses can lead to death by cardiac arrhythmia, seizures and respiratory arrest [10, 11].

Vasoconstrictor drugs were tested in anesthetized rats with ketamine/xylazine since a previous study demonstrated that this combination does not affect blood pressure [12]. Previous studies show that ketamine reduces heart rate, which was confirmed in our study. It is also known that ketamine does not change norepinephrine's effect of increasing heart rate [13]. The basal heart rate in awake rats ranges from 300 to 400 bpm; ketamine/xylazine anesthesia significantly reduced heart rate (around 200 bpm). Xylazine is an α_2-adrenoceptor agonist, thus binding to presynaptic receptors that would promote negative feedback to

sympathetic release of norepinephrine [14]. However, this feedback would only be triggered in the model used in the present study if an electrical stimulation approach was used. On the other hand, xylazine interaction with post-synaptic receptors would have promoted generalized vasoconstriction and, therefore, an increase in basal blood pressure, which was not observed in this study.

In this study we attempted to compare epinephrine, which is the vasoconstrictor of choice for hypertensive patients according to the American Heart Association (AHA) [3], with felypressin, which is a less studied non-adrenergic vasoconstrictor that acts through interaction with V_1-vasopressin receptors [2]. It is known that adrenergic agonists used as vasoconstrictors can develop pronounced side effects on the cardiovascular system in children [15] and on the metabolism, such as increase in blood glucose levels and reduction in potassium levels in healthy volunteers [16]. The AHA indicates a maximal dose of 56 μg epinephrine in cardiovascular patients [3]. It is important to clarify that higher doses of drugs are necessary for safety tests in rodents due to interspecies differences in cytochrome P450-mediated drug metabolism (because of their faster metabolism as compared with humans) [17]. In the present study, epinephrine doses ranged from 0.08 to 1.2 μg, considering weight correction from rats to humans (233.33 times); such doses corresponded to 1–16 times the epinephrine content in local anesthetic cartridges. Felypressin had a similar correspondence ranging from 2 to 16 times the content of local anesthetic cartridges (0.054 IU). Another point that must be considered is that the administration route was an intravenous injection, which is mostly an accidental event in routine dental procedures.

Epinephrine's hypotensive response is related to the interaction with β_2-adrenoceptors. In our study, non-treated hypertensive animals showed a more pronounced vasodilator effect. This confirms that epinephrine is able to compensate the vasoconstriction and cardiac effects, thus normalizing blood pressure levels in hypertensive patients [18]. On the other hand, felypressin produced no significant vasodilation; this lack of hypotensive action is expected since the vascular action of this drug relies on binding to V_1-vasopressin receptors [2].

The efficacy of both vasoconstrictor drugs was proven by the non-significant differences of hypertensive effect for the majority of comparisons for similar doses of epinephrine and felypressin (Table 2). As is widely known, epinephrine increases heart rate by β_1-adrenoceptor binding, which is blocked by atenolol administration. Felypressin reduced heart rate only in the normotensive group; thus we suggest that this effect is a compensatory response promoted by vasoconstriction and increased blood pressure values (Fig. 5). This suggests that vasoconstriction is the only mechanism to increase blood pressure in the felypressin experiments. Other studies have showed that felypressin significantly reduced cardiac rate in isolated rabbit heart at a dose of 1.6 IU, and reduced contraction force at a dose of 5.5 IU [19]; felypressin also increased cardiac arrest produced by prilocaine in isolated hearts [20]. Controlled hypertensive patients showed a higher diastolic pressure during periodontal treatment with prilocaine anesthesia associated with felypressin than with prilocaine alone [21].

The 1K1C hypertension model is closely related to human essential hypertension. Atenolol was chosen because of its wide use in the treatment of hypertension in humans, and also because it produced a more pronounced hypotensive effect in another study with a similar hypertension model in rats [8]. Atenolol-treated rats showed reduced blood pressure when compared with hypertensive non-treated ones, but values were still higher than normotensive controls. Drug interactions between epinephrine and non-selective β-blockers may induce pronounced bradycardia, dose-dependent elevation of blood pressure [22, 23] and increased duration of anesthetic effect [24]. In our study, the reduced vasodilator response in 1K1C atenolol-treated rats indicates that receptor selection may be reduced depending on the dose, since we used a high dose of atenolol (90 mg/kg). 1K1C atenolol-treated rats showed significantly reduced hypertensive responses to both vasoconstrictors tested, which surprisingly suggests that atenolol β-blockade may be also important for felypressin's cardiovascular effect, as is widely known for epinephrine. To the best of our knowledge, our study is the first to demonstrate such an interaction. Further studies will be needed to investigate this possible interaction mechanism.

Although felypressin is not involved in essential hypertension development [25] and has no effect on adrenoceptors, it interacts synergistically with epinephrine to increase heart rate and decrease mean blood pressure (as opposed to an increase in mean blood pressure evoked by epinephrine alone) [26]. The reduced hypertensive effect suggests that felypressin may be safe for hypertensive patients using atenolol or other β-blockers.

Felypressin's biological half-life ranges from 17 to 35 min, and it is expected that peptidases present in tissues are able to metabolize this molecule [27]. The response duration seems to be the most pronounced difference between epinephrine and felypressin. Blood pressure recording showed a peak pattern in epinephrine's hypertensive response (Fig. 1a), while felypressin showed sustained responses (Fig. 1b). This must be considered, since tachycardia associated with hypertensive crisis denotes heart complications such as left ventricle failure [28].

In an attempt to extrapolate to the clinical setting, our data suggest that epinephrine use in hypertensive patients treated or not with atenolol is safe if limited to three anesthetic cartridges, as recommended by some authors [3, 18], but that felypressin may also be a safe vasoconstrictor for this population due to prolonged vasoconstriction and reduced number of cardiovascular side effects. More importantly, our results strongly suggest that intravascular injection of isolated vasoconstrictor drugs such as epinephrine and felypressin does not cause significant changes in hemodynamic parameters; therefore the administration of local anesthetics without a vasoconstrictor agent does not seem to be an advantage even in non-controlled hypertensive patients.

Our study demonstrated that after intravenous injection felypressin is as efficient as epinephrine in inducing increases in blood pressure in normotensive and 1K1C hypertensive rats treated or not with atenolol. Atenolol significantly reduced such hypertensive responses to both felypressin and epinephrine. Therefore, our study is the first to demonstrate that atenolol β-blockade may be also important for felypressin's cardiovascular effect, as is widely known for epinephrine. Felypressin did not produce a marked hypotensive action and evoked a longer increase in blood pressure as compared with epinephrine in normotensive and hypertensive 1K1C rats treated or not with atenolol.

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Conflict of interest All the authors declare no conflict of interest. Pedro C. Lomba works at Dentsply Pharmaceutical Ltda.

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