

Felypressin Increases Blood Pressure During Dental Procedures in Hypertensive Patients

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Abstract

Background: Felypressin has been added to local anesthetic to increase the length of the anesthetic effect and reduce toxicity during dental procedures. However, the effect on blood pressure remains uncertain, and this may be highly relevant in the dental treatment of hypertensive patients.

Objective: To investigate the effect of felypressin on blood pressure in hypertensive patients with controlled BP.

Methods: 71 subjects with these characteristics and in need of periodontal treatment were studied. After 10 minutes of rest, local anesthesia (prilocaine) was infiltrated with and without addition of felypressin. Then, a deep subgingival scaling was performed. Blood pressure was measured by an automated oscillometric device (DIXTAL DX2010). Ten minutes after the administration of the anesthetic, peak anesthetic action was recorded. The State-Trait Anxiety Inventory (STAI) was used to assess the patients' trait anxiety.

Results: Systolic blood pressure increased after anesthesia, regardless of association with felypressin, throughout the dental procedure ($p < 0.05$) and this response can be explained, at least in part, by the trait anxiety levels of the subjects. However, a further increase in diastolic blood pressure was observed when prilocaine was associated with felypressin ($p < 0.05$), but this response did not change with trait anxiety levels.

Conclusion: Felypressin increased the diastolic blood pressure of hypertensive patients with controlled blood pressure. Patients with high trait anxiety presented increases in systolic blood pressure upon some procedures, suggesting that an increase in blood pressure might also be related to fear or anxiety. (Arq Bras Cardiol 2012;99(2):724-731)

Keywords: Felypressin; blood pressure; anesthesia, local; hypertension; periodontal diseases.

Introduction

Felypressin is a synthetic hormone of the posterior pituitary lobe characterized by vasoconstrictor properties that is widely used in dental procedures¹. Its vasoconstrictor action seems to be mediated by V1 receptors of the blood vessel smooth muscle cells². However, it is noteworthy that the V1 receptor-mediated vasoconstrictor action is dependent on territory, since vessels of skeletal muscles and skin are more sensitive than renal vessels². Anyway, felypressin has been widely added to local anesthetic solutions to increase the duration of the anesthetic effect and reduce the risk of toxicity during dental procedures³. Since its benefits are undeniable, its use is recommended by the Therapeutic Council of Dentistry of the United States of America³ in association with all local anesthetics, because the absence of a vasoconstrictor promotes fast absorption of the anesthetic and, consequently, low anesthetic effectiveness.

In Brazil, where hypertension affects 22-44% of the adult population⁴, dental surgeons frequently have to provide dental care to hypertensive patients. However, despite the aforementioned benefits for dental procedures, it is not yet clear if felypressin in addition with prilocaine increases arterial blood pressure (BP), especially in subjects with special conditions, as is the case of hypertensive patients^{5,6}. Is true that the level of the felypressin-related blood pressure increases might be low; nonetheless, some subgroups such as hypertensive subjects may benefit from efforts to reduce a further felypressin-related cardiovascular risk. Furthermore, that the choice of the local anesthetic seems to influence the hemodynamic response during dental procedures^{7,8} and, therefore, in the absence of any interaction with adrenergic receptors, it has been suggested that felypressin presents a lower incidence of side effects on hemodynamic responses⁹. For all these reasons, it is important to investigate the effect of felypressin on BP in hypertensive patients.

Another aspect to be considered is the individual response to stress during dental procedures. It is known that the response to a particular stressor stimulus is greater in hypertensive than in normotensive subjects¹⁰. Therefore, the possible pain caused by dental procedures without anesthesia or even in situations of ineffective anesthesia can produce stress for the patient, resulting in the release of endogenous catecholamine, which sometimes reaches higher levels than

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the aggregate amount contained in a tube of anesthesia¹. Thus, dental procedures also might increase BP as a result of fear or anxiety¹¹, in addition to a possible increase in BP due to the action of felypressin¹², especially in hypertensive patients.

We hypothesized that BP might increase in the presence of felypressin during dental procedures, and the aim of this study was to investigate the effect of anesthesia, associated or not with felypressin on the BP of drug-controlled hypertensive patients during periodontal treatment.

Methods and Materials

The present study was performed as an open-label, randomized, two-way, two-treatment, single-dose study, after two hours of fasting, and the treatments were separated by a wash-out period of 10 minutes between the interventions (prilocaine or prilocaine plus felypressin) to comply with the crossover method proposed. Each subject was assigned a unique identification number and during the entire study, all the procedures were carried out by the same researchers, with a standardized protocol. The procedures were performed in accordance with the guidelines of the Helsinki Declaration for human experimentation and approved by the Ethics Committee of the General Hospital of the University of Sao Paulo, Brazil. All volunteers signed an informed consent form prior to their participation. The experimental design is present in Figure 1.

Subjects

Seventy-one hypertensive patients under antihypertensive treatment and with controlled BP as evaluated upon their last medical visit (systolic and diastolic BP lower than 140/90 mmHg, respectively) were investigated. The sample included patients of both genders in need of periodontal treatment. Patients who presented diabetes mellitus, renal, coronary, heart or liver failure, and pregnant women were excluded.

Preliminary assessments

All patients underwent an initial dental examination. At arrival at the dentist's office, they were placed to rest, seated

in a comfortable dentist's chair with the back at an angle of 45° for 10 minutes. After this, their trait anxiety level was assessed and they were classified as patients with low or with high anxiety level. Subsequently, the dentist performed the assessment of oral health and verified the presence of periodontal disease. For this purpose, periodontal disease was diagnosed according to the periodontal index criteria (Periodontal Screening & Recording - PSR). Briefly, this index identifies the presence of gingival inflammation and of aggravating local factors such as plaque and tartar attacking the gingival and periodontal tissue¹³. Patients who did not fulfill these criteria were excluded. Then, to familiarize them with the procedures, all patients were submitted to subgingival scaling without anesthetic procedures, since subgingival scaling is not painful.

Anxiety assessment

The State-Trait inventory (STAI)¹⁴ was used to assess the patients' anxiety level. This inventory is composed of two parts, with 20 statements each, and determines how the person usually feels in his/her life based on a scale, with a score range from 20 to 80. Thus the patients were classified according to their score as presenting "low anxiety" (score below or equal to 25) or "high anxiety" (score above 25).

Blood pressure

During the experimental session, BP was measured in a triplicate way and the mean was calculate for each period (rest, local anesthetic, subgingival scaling and anesthetic peak) with an automated oscillometric device (DIXTAL - model DX 2010, São Paulo, Brazil) that is the result of the perfecting of DIXTAL - model DX 2710¹⁴, validated according to the international regulations¹⁵. The cuff used was the adequate size for the circumference of the patient's dominant arm: a) "adult" cuff with a 13 x 24cm inflatable bag for patients with arm circumference of 24 x 32cm; and, b) "obese" cuff with a 17 x 32cm inflatable bag for patients with arm circumference of 32 x 42cm. During the measurement, the cuff was positioned on the arm and adjusted for the height of the left ventricle¹⁶.

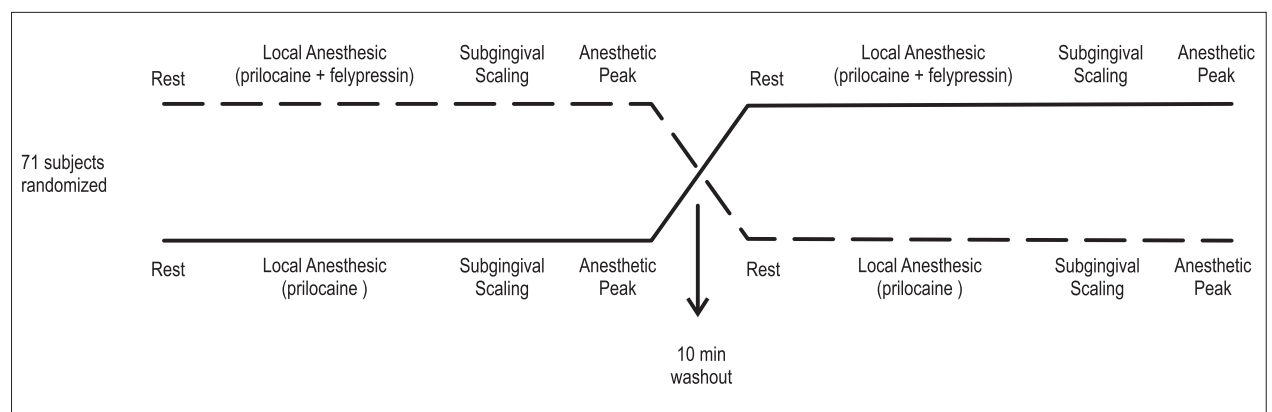


Figure 1 - Experimental design

Periodontal treatment

During the periodontal treatment, all patients were instructed to take their antihypertensive drugs at 8:00 am, to ensure the antihypertensive action at the same time of the experimental session. The patients arrived at the dental office at 2:00 pm, after a postprandial period of 2 hours, in order to prevent any effect of food on BP.

During the pre-intervention period, defined as REST, the patients were seated in a comfortable dentist's chair with the back at an angle of 45° for 10 minutes, during which their BP was measured every two minutes. Then, the local anesthetic (prilocaine), with or without felypressin, was infiltrated using a syringe with a 30G carpule needle. This procedure was named as LOCAL ANESTHETIC period and lasted four minutes. The quantities used were 144mg 4% prilocaine without felypressin (2 tubes) and 108mg prilocaine with 0.11 UI of felypressin (2 tubes), totaling four tubes. It is noteworthy that the difference in the amount of prilocaine is due to commercial availability of local anesthetic, in which is only found prilocaine 3% with felypressin 0.03 IU, and prilocaine 4% without vasoconstrictor. During this step, BP was measured twice. After the anesthesia, the technical procedure for deep subgingival scaling was performed and BP was again measured every two minutes. This dental procedure, defined as SUBGINGIVAL SCALING period, is always painful and justifies the use of an anesthetic. The anesthetic peak of prilocaine or prilocaine associated with felypressin was reached 10 minutes after the anesthetic injection, and BP was measured twice. This period was defined as ANESTHETIC PEAK period. The instruments used during the deep subgingival scaling were McCall and Grayce curettes, sickles of the type scraped, and periodontal probes.

Anesthetic simulation

A subsample of 34 patients was invited to engage in an anesthetic simulation session one week before the experimental session, in which an anesthetic simulation with an empty syringe and needle was performed, in order to evaluate the effect of the procedure on BP. The details of the anesthetic simulation session were as described: rest, evaluation of oral health, and subgingival scaling in the preliminary assessments. This procedure was performed one week before the experimental session, immediately after the dental evaluation to assess the need for dental treatment.

Statistical analysis

Considering a power of 80% and an alpha error of 5%, the minimal sample size necessary to detect a difference of 10 mmHg in BP was calculated to be 37 subjects.

Data normality was checked by means of the Shapiro-Wilks test, using the statistical package SPSS for Windows (Statistical Package for Social Sciences, version 13.0, Chicago, IL, USA).

The effects of prilocaine associated or not with felypressin were compared by a two-way ANOVA test for repeated measures, establishing anesthetic (prilocaine or prilocaine + felypressin) and stage (rest, anesthetic, subgingival scaling and anesthetic peak) as the main factors. Post-hoc comparisons were made using the Newman-Keuls test. Values of $p < 0.05$ were considered statistically significant, and data are presented

as means and standard error. The software package used for these analyses was STATISTICA (Statistic for Windows 4.3, StatSoft Inc, Tulsa, OK, USA, 1993).

The primary outcomes were changes in office BP during painful dentistry procedures and the effects of prilocaine associated or not with felypressin.

Results

Seventy-one hypertensive patients (44 women and 27 men) with BP controlled by antihypertensive treatment and in need of periodontal treatment completed the study. The characterization of the sample is presented in Table 1. It is noteworthy that the trait anxiety was measured in 36 patients only, because the other volunteers did not fulfill the forms completely.

The effects of the anesthetic simulation session are presented in Figure 2.

During the anesthetic simulation session, both systolic and diastolic BP increased significantly ($p < 0.05$) compared to the other steps of the session (rest, assessment of oral health, and subgingival scaling).

Figure 3 shows the effect of anesthetic added or not with felypressin on BP. Regarding systolic BP, a significant effect of the stage factor was identified, since prilocaine, associated or not with felypressin, increased the systolic BP throughout the

Table 1 – Demographic characteristics of the sample

	n (%)
Patients	71
Male	27 (38)
Female	44 (62)
Age (y)	48±12
BMI (kg/m²)	28.1±4.9
< 30 kg/m ²	59 (83)
> 30 kg/m ²	12 (17)
Ethnic group	
Caucasian	40 (56)
Non-Caucasian	31 (44)
Classes of antihypertensive drugs	
Angiotensin II blocker	15 (21)
Calcium channel antagonist	25 (35)
Beta-blockers	34 (48)
Inhibitor of angiotensin converting enzyme	44 (62)
Adrenergic inhibitor	07 (10)
Direct vasodilators	01 (01)
Trait anxiety	36
Present	15 (42)
Absent	21 (58)

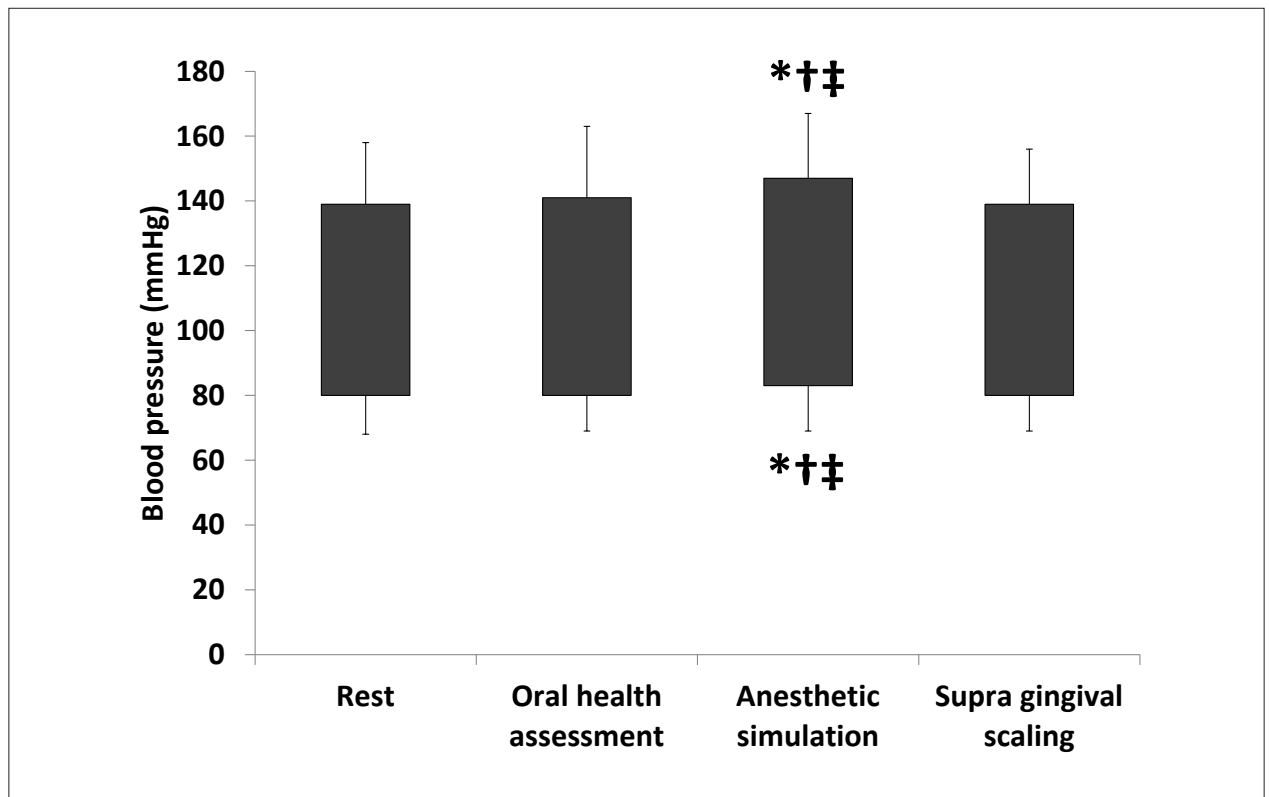


Figure 2 - Effect of anesthetic simulation on BP - Blood Pressure. In the upper and lower edge of the bar are shown the systolic and diastolic BP values (mean \pm SD), respectively. * Significantly different from rest; † Significantly different from oral health assessment; ‡ Significantly different from supragingival scaling. ($p < 0.05$).

period of the dental visit ($p < 0.05$). However, regarding the diastolic BP, a significant interaction between the main factors (condition and stage) was found. Thus, diastolic BP increased during all dental procedures under both conditions, but this increase was greater when the anesthetic was associated with felypressin ($p < 0.05$).

In a complementary analysis, subjects with low (score ≤ 25) and high (score > 25) trait anxiety were compared, and it was observed that the systolic BP increased significantly during anesthesia and subgingival scaling only in the patients with highest trait anxiety (Figure 4). However, no significant difference was observed in diastolic BP ($p > 0.05$).

Discussion

The originality of the present study is the finding that anesthetic associated with felypressin increases the diastolic BP of hypertensive patients with medication-controlled BP.

We found here that acute infusion of prilocaine associated with felypressin promotes an increase in diastolic but not in systolic BP. Our study is in agreement with that of Inagawa et al¹⁷, who found that, in male Japanese white tracheotomized rabbits, the diastolic BP increased significantly, without change in systolic BP. However, our study differs from others with human experimentation that showed that felypressin is not associated with BP increases¹⁸. This difference can be justified by the fact that we investigated hypertensive patients with

controlled BP, and the effect of felypressin might be different in hypertensive patients with uncontrolled BP, because the presence of an already elevated BP may cover up the BP response to felypressin. Furthermore, it is noteworthy that V1 receptors can trigger a powerful vasoconstrictor response¹⁹ and might therefore contribute to the tonic control of circulation, because specific antagonists of V1 receptors produce a slight, but long-lasting fall in BP². However, the effect of felypressin on the vascular tone is still a controversial issue.

The use of a local anesthetic, whether associated or not with a vasoconstrictor, in the dental care of hypertensive patients and its adverse effects on BP were evaluated by several authors^{3,16,20}, but there are no conclusive studies on this topic up to far. In the present study, we identified a BP elevation during all procedures, and a partial analysis of the data showed that this elevation tended to be more pronounced during the anesthetic procedure. Thus, two hypotheses arise: a) prilocaine also increases BP; and b) dentistry procedures are stressful enough to increase BP, regardless of prilocaine. Based on this initial analysis, we decided to include an anesthetic simulation procedure with an empty syringe and needle, to monitor the BP at the time of anesthesia. During this simulation, there was a significant elevation in systolic BP, suggesting that fear and anxiety can trigger such a response. In fact, Gortzack et al¹⁷ also demonstrated a more pronounced BP elevation during the administration of a local anesthetic, followed by reduction after removal of the needle.

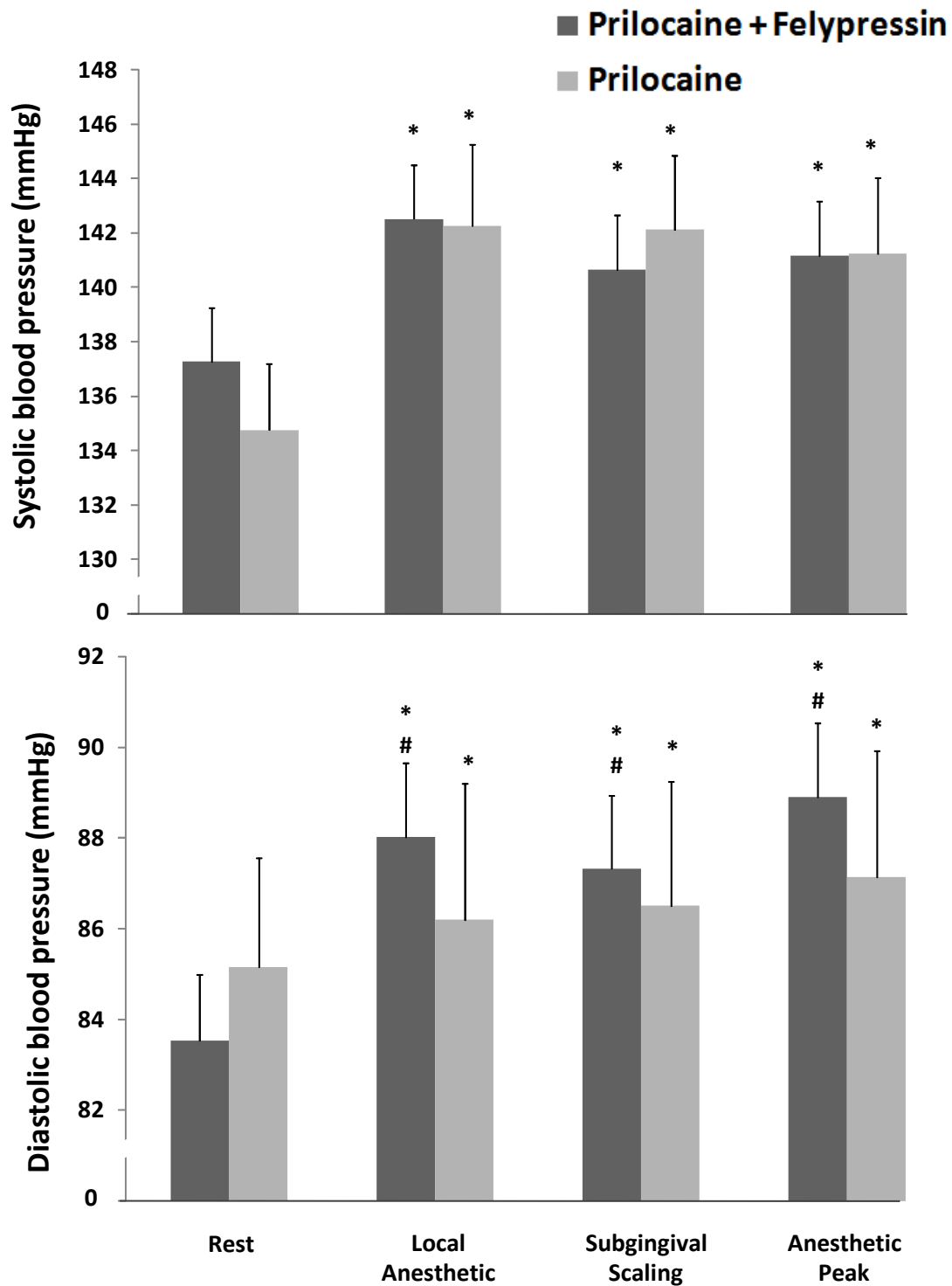


Figure 3 - Effect of felypressin on BP - Blood Pressure.
* Significantly different from rest; # Significantly different from prilocaine. ($p < 0.05$).

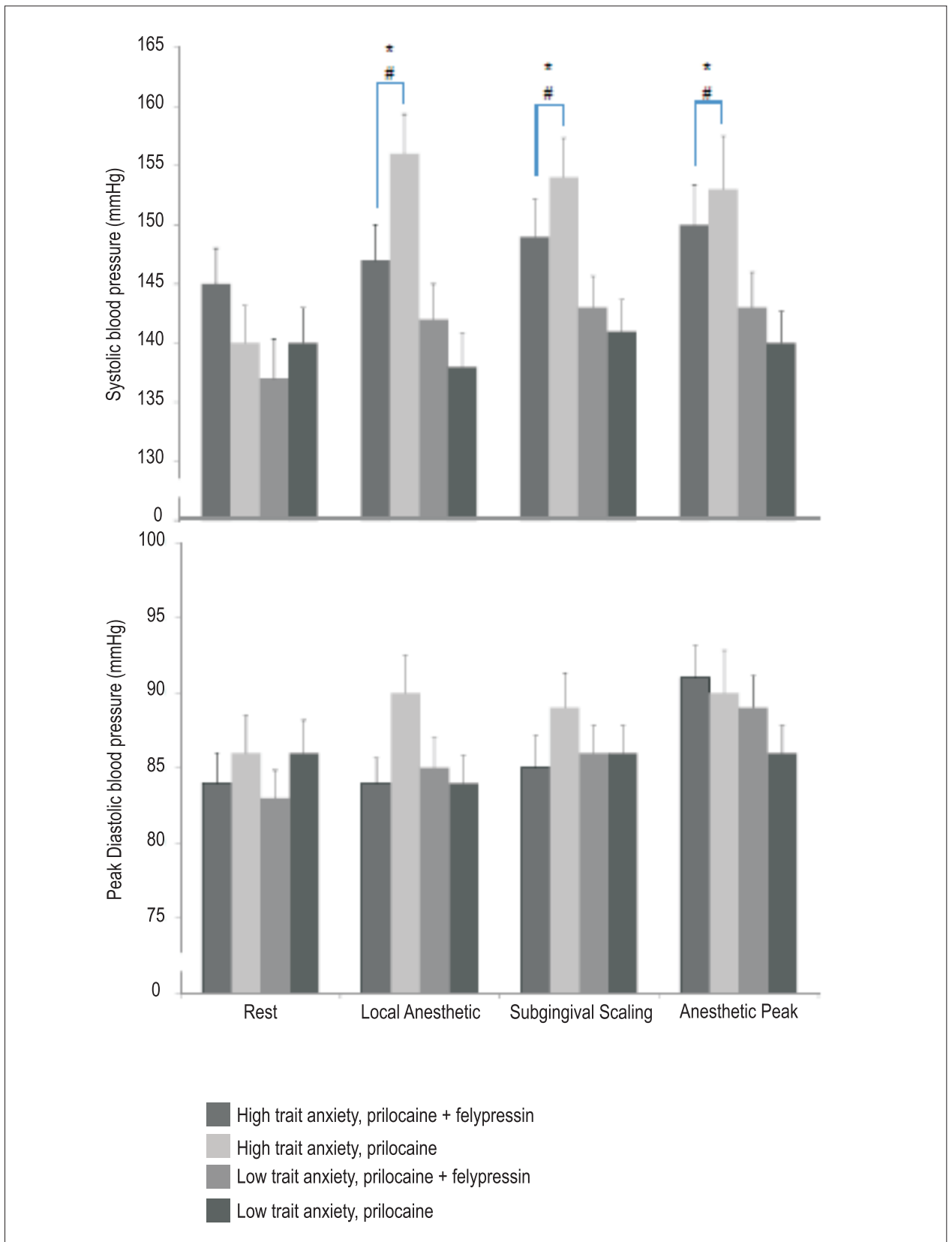


Figure 4 - Level of BP - Blood Pressure. In patients with low (n=21) and high (n=15) trait anxiety during dental procedures.
* Significantly different from the same group in the rest; # Significantly different from low trait anxiety groups, respectively (p<0.05).

It has been suggested that beta-blockers might reduce the release of endogenous adrenaline¹⁶ and, therefore, interfere with the BP response. Coincidentally, in our study, 58% of the subjects were under beta-blocker treatment and 58% of the subpopulation in which the level of stress was assessed showed mild anxiety. It is therefore possible to think that the use of beta-blockers might affect the BP responses to stress. Thus, we decided to evaluate our patients separately according to their use or not of beta-blockers (data not shown). However, no significant difference was found for either systolic or diastolic BP during the entire experimental protocol ($p > 0.05$).

It is known that the response to a particular stressor stimulus is greater in hypertensive than in normotensive subjects. Furthermore, it is noteworthy that among hypertensive patients there is variability in stress index. In a subsample of our study, 42% of the subjects were classified as high anxiety subjects and prilocaine without vasoconstrictor was found to promote a systolic BP increase (Figure 4); yet, when associated to felypressin, this response was not observed ($p > 0.05$), suggesting that blood pressure response to felypressin is not influenced by the anxiety level.

Conclusions

In conclusion, the present findings indicate that felypressin increases the diastolic BP, regardless of its anesthetic properties.

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