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Blood levels of histamine and norepinephrine in humans with sympathetic hyperactivity

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SUMMARY

The possible existence of a histaminergic pathway by which a reciprocal contralateral inhibitory modulation of the peripheral sympathetic nervous system is exerted motivated the present experimental clinical work. Blood levels of histamine (HA) and norepinephrine (NE) were measured in peripheral blood from patients with Tetanus or Guillain-Barre Syndrome (GBS), pathologies known to present sympathetic hyperactivity crisis in the course of its evolution; also in critically ill patients in general, hospitalized in Intensive Care Units (ICU); and in healthy voluntary donors from the Blood Banks. The results show that NE levels of Tetanus patients and those with GBS (336 and 326 pg/mL, respectively) were significantly higher than those of the donors and critically ill patients in general (148 and 163 pg/mL, respectively), even without being found in a crisis of clinically detected sympathetic hyperactivity, denoting the existence of a state of basal sympathetic hyperactivity in these two pathologies. Meanwhile, HA levels in these groups ranged from 7 to 10 ng/mL and showed no significant differences between them. In conclusion, the levels of HA tend to keep a dual behaviour, in those conditions with possible peripheral modulator reflex unscathed, they raised simultaneously with the levels of NE, probably as the result of the expected physiological response to situations of sympathetic stimulation; and in patients who showed an exaggerated, uncontrolled sympathetic activity, we did not observe a corresponding rise in their levels, which could be interpreted as a deficit of the modulating response.

Key words: *Histamine, norepinephrine, peripheral sympathetic control, tetanus, Guillain-Barre syndrome, hypersympathetic activity, essential arterial hypertension.*

RESUMEN

La posible existencia de una vía histaminérgica, mediante la cual se ejerce una modulación inhibidora recíproca contralateral del sistema nervioso simpático periférico, motivó el presente trabajo clínico experimental. Se determinaron los niveles sanguíneos de histamina (HA) y norepinefrina (NE) en sangre periférica de pacientes con Tétanos o con Síndrome de Guillain-Barré (SGB), patologías que se sabe que presentan crisis de hiperactividad simpática en el curso de su evolución; igualmente en pacientes críticamente enfermos en general, hospitalizados en Unidades de Cuidados Intensivos (UCI); y en donantes voluntarios sanos de Bancos de Sangre. Los resultados muestran que los niveles de NE en pacientes con tétanos y aquellos con SGB (336 y 326 pg/mL, respectivamente) fueron significativamente más altos que los de donantes y pacientes críticos en general (148 y 163 pg/mL, respectivamente), incluso sin presentar una crisis de hiperactividad simpática detectada clínicamente, denotando la existencia de un

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estado de hiperactividad simpática basal en estas dos patologías. Mientras que los niveles de HA obtenidos en estos grupos oscilaron entre 7 y 10 ng/mL y no mostraron diferencias significativas entre ellos.
En conclusión, los niveles de HA tienden a mantener un comportamiento dual, en aquellas condiciones con posible reflejo modulador periférico intacto, los niveles de HA se elevan simultáneamente con los niveles de NE, posiblemente como la respuesta fisiológica esperada a situaciones de estimulación simpática; y en pacientes que mostraron una actividad simpática exagerada e incontrolada, no observamos la correspondiente elevación de sus niveles, lo que podría interpretarse como un déficit en la respuesta moduladora.

Palabras clave*: Histamina, noradrenalina, control simpático periférico, tétanos, síndrome de Guillain-Barré, hiperactividad simpática, hipertensión arterial esencial.*

INTRODUCTION

The peripheral circulation is, in essence, under a dual control: through the central nervous system and peripherally through local control because of the metabolic conditions prevailing near the blood vessels in each tissue. The predominance of one or the other control depends on each tissue. Thus, in some regions such as skin and splanchnic regions, nervous regulation predominates, while in others such as the brain and heart local regulation predominates (1,2). Most of the arteries and veins in the body are innervated, to varying degrees, by fibers from the sympathetic nervous system, which exert a tonic effect on the blood vessels. The activity of sympathetic fibers in a direct or reflex way increases vascular resistance to blood flow. On the other hand, the vascular smooth muscle responds to humoral stimulation by drugs and hormones without evidence of electrical excitation. This has been called pharmacomechanical coupling, with the participation of substances such as catecholamines, histamine, acetylcholine, serotonin, angiotensin II, adenosine, and prostaglandins (3). Local changes alter the contractile state of vascular smooth muscle, and alterations such as temperature increase, acidosis, or increased levels of carbon dioxide (CO_2) induces relaxation of this tissue (2,4). Moreover, endothelium, initially considered as a cell monolayer that covered the vasculature, serving as a barrier between blood and the vascular wall (5), has now been considered as an organ that regulates vascular homeostasis (6).

The extrinsic control of the peripheral circulation results from the combination of constrictive influences of the sympathetic system on the resistance vessels and on the capacitance vessels, the effect of active type sympathetic vasodilation, parasympathetic influences on some regional blood beds, humoral factors and vascular reflexes, always existing a balance between extrinsic and intrinsic factors in the regulation of peripheral blood flow (7-9).

There are also two other active vasodilator mechanisms mediated through the peripheral sympathetic system. One produces slow vasodilation in the presence of adrenergic blockers; and another that produces transient active vasodilation in response to the stimulation of baroreceptors or a direct sympathetic regulation which the postulated neurotransmitter is histamine (10).

The physiological role of the histaminergic regulation is still a matter of research; in this regard, Campos (11-18) postulated a regulatory histaminergic pathway of peripheral sympathetic activity, which was shown in different animal models *in vivo* and tissue preparation (19-22). This evidence served as a source of motivation for the present work, as a contribution to support with clinical experiments the existence of such histaminergic inhibitory regulation.

For the aforementioned, we aimed to support experimental clinical tests the existence of a histaminergic interneuron as a peripheral reflex that interacts with the sympathetic terminals to modulate and maintain homeostasis. To achieve this goal, we assessed HA and NE levels in the blood of critical patients hospitalized in the UCI, in voluntary blood donors, and critically ill patients with tetanus and GBS, both in stable conditions and during sympathetic hyperactivity crises. We hypothesize that HA levels must follow those of NE during sympathetic activity since the release of neuronal HA is part of a peripheral compensatory reflex of sympathetic activity. Thus, in situations of absence, failure, or deterioration of said reflex, HA levels must be depressed with the consequent increase in NE levels, as expressed during sympathetic

hyperactivity crises.

The data from the present work, unpublished until now, was carried out under the guidance of Dr. Homero Augusto Campos, developing the experimental phase in the Laboratory of Neurochemistry that he directed at Medical School José María Vargas, Universidad Central de Venezuela. We dedicate this work to his memory, with our eternal gratitude and affection.

MATERIAL AND METHODS

63 subjects of both genders participated in the study, divided as follows: critically ill patients in general (n=31), affected patients with tetanus (n=6), affected patients with GBS (n=5), and donors from a Blood Bank (n=21). Bioethics Committee of the University Hospital of Caracas approved all procedures and protocols which complied with the Declaration of Helsinki for experimentation with human beings (1975 and revised in 1983). Subjects were informed about the characteristics and importance of the study and written informed consent was obtained from patients or the legal guardian, and donors, required by human research standards.

Venous blood samples were withdrawn through central or peripheral venoclysis, and the blood samples obtained were collected in a tube containing 0.2 mL of 5 % EDTA in physiological solution (NaCl 0.9 %) were divided into two aliquots, 5 mL each, for their treatment, conservation, transport, and subsequent quantification of neurotransmitters; observing strict compliance with the necessary cold chain, and in a transfer time that in no case exceeded one hour.

The treatment and purification of blood samples for the determination of HA levels was performed according to the method of Schwartz (23), modified and adapted by Campos (12). Briefly, the blood sample for histamine was centrifuged at a speed of 10,000 rpm at 4 °C, for 15 minutes. Then, the supernatant of each sample was stored in hermetically sealed plastic tubes at a temperature of -80 ºC, until the moment of processing. The samples were analyzed by fluorometry, in a Perkin Elmer LS 50B luminescence spectrometer, at 354 nm of excitation and 450 nm of emission, and the results were expressed in nanograms per milliliter (ng/mL). For NE determination, the sample was subjected to purification with alumina adsorption according to the method of Lake (24), and NE was assessed using high-efficiency liquid chromatography (HPLC) with electrochemical detection (Waters model 464) with an electrochemical detector (Millipore) and SSI pump 222 D coupled to data acquisition and processing system for "EZCHROM" chromatography (Scientific Software Inc). The mobile phase was specially prepared for the detection of catecholamines, and the results were expressed as pg/mL.

The guarantee that the state of sympathetic hyperactivity in the patients who presented it was primary or inherent to their disease, and not secondary to reactions due to hypoxia, pain or anxiety, was obtained by taking care of the samples during adequate sedation and analgesia, oxygenation monitoring, and Valsalva maneuver (25,26), to rule out the presence of hypoactivity or parasympathetic failure, by applying the Valsalva index or ratio (27,28). To do this Valsalva maneuver, the method was modified or adapted for its realization in an unconscious and intubated patient that consisted of generating the positive pressure using a resuscitation balloon ("Ambú"© type) stripped of the exhalation valve and connected to the endotracheal tube or tracheostomy on one side, and the pressure gauge circuit on the other, through a "T" tube. This while performing a restriction of abdominal inspiratory incursion by manual compression and simultaneous electrocardiographic recording performed to obtain RR intervals and the Valsalva index or ratio.

The data were expressed as mean ± standard deviation of the mean, and were analyzed by one-way analysis of variance (ANOVA), with Bartlett's test to establish its homogeneity; and multiple comparisons were performed with "Student t-test" for paired samples and Newman Keuls' test among the groups. A value of $P<0.05$ was considered significant. The correlation coefficient between the values of HA and NE in the different groups studied was also determined with the Pearson test. All statistical analysis performed was done using the IBM Pi-Stat program.

RESULTS

NE and HA blood levels. As shown in Table 1 and Figure 1, in critical patients and blood donors, the average of the NE values was similar and with a substantial dispersion, while in the tetanus patients and those with GBS, significantly higher values obtained, although equally dispersed in the case of tetanus. HA values did not show significant differences between these groups.

Table 1

Norepinephrine (NE) and histamine (HA) levels in blood according to groups of patients studied

	NE (pg/mL)	HA (ng/mL)
Critical patients	**163,62** ± 103,34 (n = 30)	**10,03** ± 8,05 (n = 24)
Donors in blood banks	**148,38** ± 56,62 (n = 21)	**9,96** ± 4,77 (n = 20)
Patients with tetanus	**335,83** ± 63,5 (n = 6)	**9,07** ± 1,83 (n = 6)
Patients with GBS	**226,0** ± 21,6 (n = 5)	**6,6** ± 1,33 (n = 5)

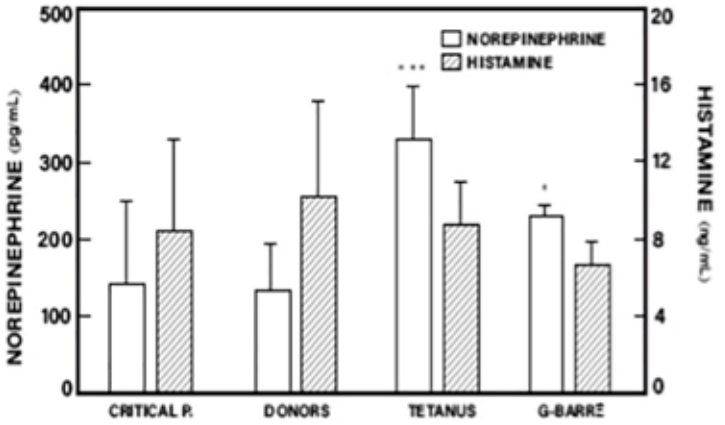

Figure 1. Norepinephrine (NE) and histamine (HA) levels in blood according to the patient group studied. n=5-30, *P<0.05 (G-B vs T); ***P<0.001 (T vs C and D).

HA and NE levels in critically ill patients according to their sympathetic activity. We selected the critical patients who presented high levels of NE or high levels of systolic/diastolic blood pressure (SAP/DAP) and heart rate, and grouped them as critical patients with high sympathetic activity (HSA); and to those who showed these low values, such as low sympathetic activity (LSA). Critical patients with HSA (n = 9) presented the following diagnoses of admission to the ICU: firearm paraplegia injury, porto-cava bypass/portal hypertension (liver

cirrhosis), upper gastrointestinal bleeding/caustic intake, cerebrovascular accident hemorrhagic, craniocerebral trauma, hemorrhagic pancreatitis, and active lupus/pneumonitis. In this patient, NE mean values were 214.9 ± 51 pg/mL, and that of HA 9.29 ± 3.5 ng/mL. Critical patients with LSA (n = 4) corresponded to the following diagnoses of admission to the ICU: sepsis/abortion, polymyositis, myasthenia/sepsis due to pneumonia and eclampsia with multiorgan failure; and showed the following NE and HA blood levels: 39.5 ± 23.81 pg/mL, and 3.72 ± 0.5 ng/mL, respectively (Figure 2).

Correlation between HA and NE blood levels in the studied groups

Critical patients. There was no significant correlation between the values of NE and HA in critical patients (Figure 3). Critical patients (n=10) correspond to those in which it was determined both amines in the blood samples.

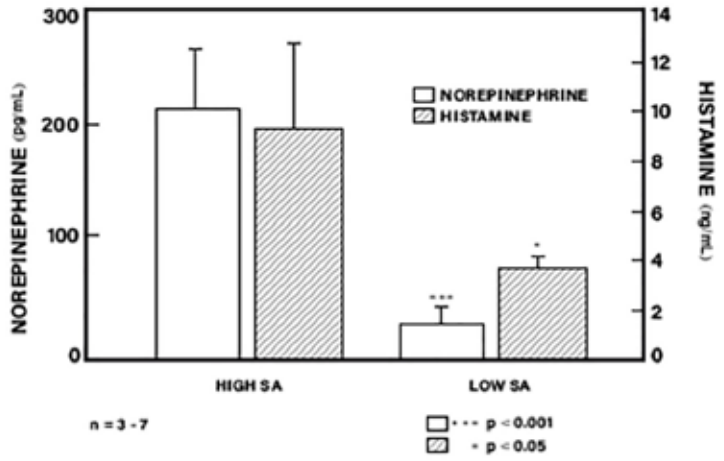

Figure 2. Blood levels of NE and HA in critically ill patients according to their sympathetic activity (SA).

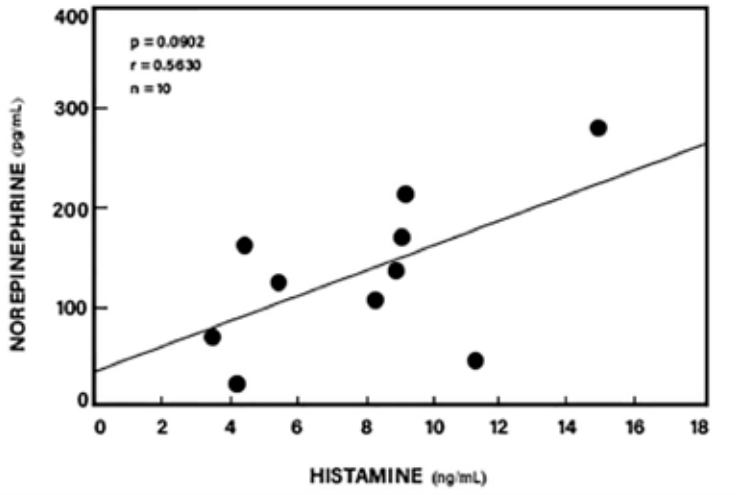

Figure 3. Correlation between the values of HA and NE obtained in critical patients.

Blood Bank donors. The results demonstrate that NE levels were inversely and significantly correlated with HA levels (r = -0.8895; P<0.0001) (Figure 4).

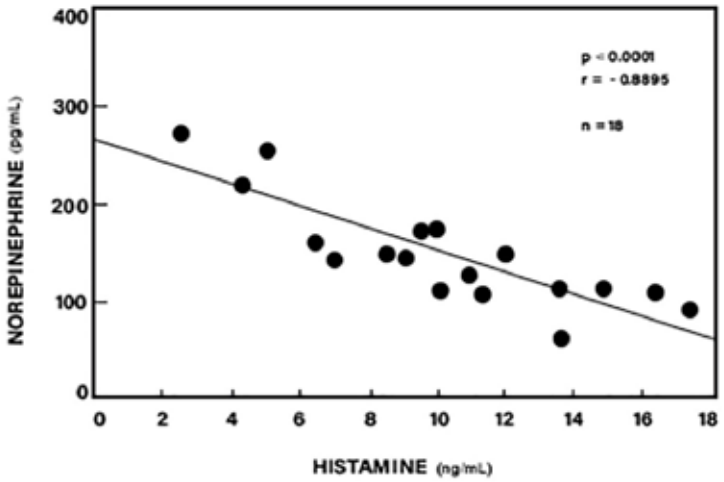

Figure 4. Correlation between blood levels of HA and NE in blood bank donors.

Patients with tetanus and GBS. Correlations analysis between NE and HA levels in tetanus and GBS patients shows that NE was positively and significantly correlated with HA blood levels (r = +0.9126; P<0.0001) (Figure 5).

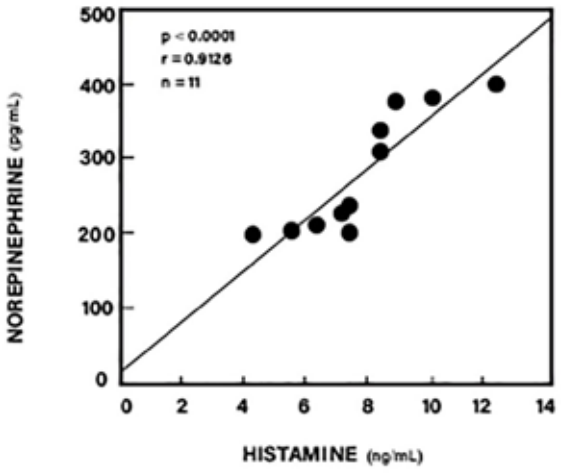

Figure 5. Correlation blood values of HA and NE in tetanus and GBS patients.

Furthermore, this correlation was also observed when the results were represented separately in patients suffering from tetanus and those with GBS, is also positive and significant (P<0.0138 and P<0.0589, respectively) (Figure 6).

Blood levels of HA and NE in patients who presented a sympathetic hyperactivity crisis. During the period of sampling, this condition only appeared in two of the tetanus patients, so it is not feasible to establish a statistical analysis of the values obtained. However, the NE values were almost triple the level shown by the tetanic patients in baseline conditions (Table 1, Table 2, and Figure 7).

It is noteworthy that even at 1 hour after the sympathetic hyperactivity was controlled clinically, these high levels of blood NE were maintained. It can see that levels of HA in these patients remained close to the average of the control groups.

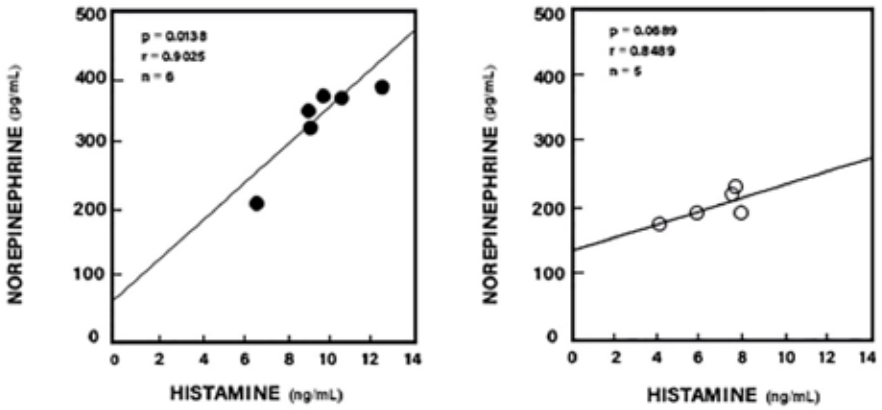

Figure 6. Correlation between blood levels of HA and NE in patients with Tetanus and with GBS presented separately.

Table 2

Norepinephrine (NE) and histamine (HA) blood levels of tetanic patients during sympathetic hyperactivity crisis

	NE (pg/mL)	**HA (ng/mL)**
Sympathetic hyperactivity (before treatment)	**855,5** ± 140,7 (n = 2)	**13,04** (n = 1)
Sympathetic hyperactivity (after treatment)	**852,0** ± 97,6 (n = 2)	**8,62** ± 0,69 (n = 2)
Post sympathetic hyperactivity	**758,5** ± 2,12 (n = 2)	**9,26**] 4,32 (n = 2)

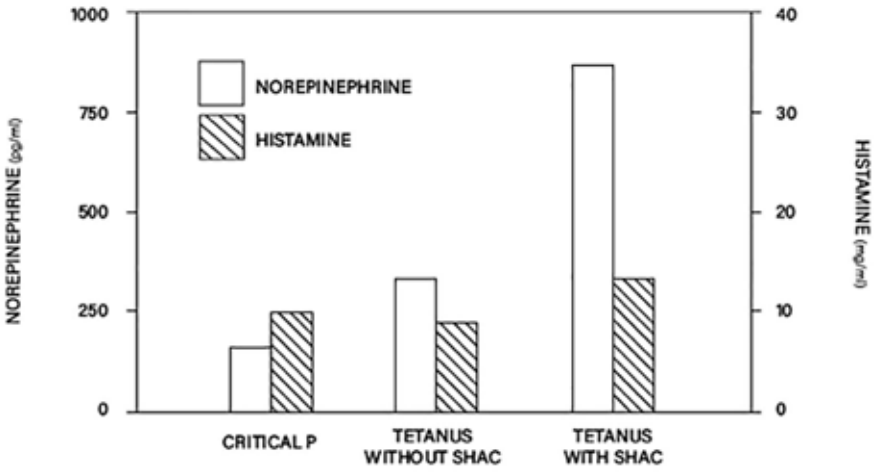

Figure 7. Norepinephrine (NE) and histamine (HA) levels in the blood of tetanus patients with and without sympathetic hyperactivity crisis (SHAC), and critically ill patients in general (Only in absolute values of the average).

Oxygenation level and Valsalva ratio in patients with sympathetic hyperactivity

Both controls were carried out both in tetanic patients and patients with GBS in their baseline conditions, as in tetanus patients who developed frank, sympathetic hyperactivity. In them, the average Inspired Oxygen Fraction (FiO_2) was 0.35±0.11, and the blood pressure of O_2 and CO_2 (mmHg) was 93 ± 9 and 32 ± 4, respectively. Thus, the hypoxia factor was ruled out as a possible inducer of increased sympathetic activity.

In all of them, the Valsalva Index was more significant than 1.2, which ruled out the presence of failure or parasympathetic insufficiency in the patients studied.

Blood pressure and heart rate. In Figure 8 are shown the values of SAP, DAP, and HR. There was no significant difference between the groups studied.

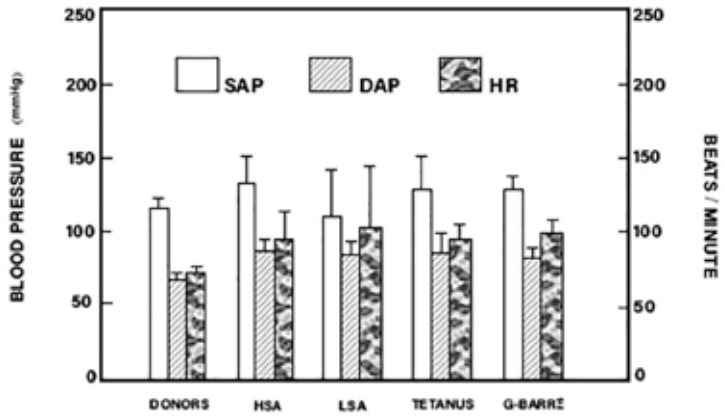

Figure 8. Arterial pressure (SAP = systolic, DAP = diastolic) and heart rate.

DISCUSSION

At present, studies about neurohumoral activation of the peripheral circulation and its participation in both pathophysiology and the prognosis of critical conditions of various diseases and organic failures are still needed. Moreover, it is accepted that activation is synonymous with increased activity of the two principal vasoconstrictor systems: the sympathetic nervous system and the renin-angiotensin-aldosterone system (2,29).

Most of the research focused on the physiology, pathophysiology and pharmacological inhibition of both systems and, in fact, the documentation of a clinically significant reduction in morbidity and mortality after the beta-adrenergic blockade and prompt inhibition of the angiotensin-converting enzyme in acute myocardial infarction, underlines the importance of these two systems (30,31).

In addition to the classic neurohumoral systems, in the 1980-1990s, it was determined that the heart and vascular endothelium could synthesize and secrete peptides with potent biological actions. Not only was demonstrated the existence of a cardiac renin-angiotensin system (32), but also that the cardiomyocytes produce a family of peptide hormones with a vasodilator, natriuretic and diuretic properties (33), and that the endothelial cells produce, in addition to a variety of non-peptide vasoactive substances, also secretes a vasoconstrictor peptide known as endothelin (34). Within this approach, there is

still an essential relationship between circulating catecholamines and mortality in various diseases such as hypertension, diabetes, myocardial infarction, heart failure, and shock (35-38).

Several mechanisms could contribute to this prognostic influence of circulating catecholamines. Myocardial oxygen consumption elevates heart rate due to the increase in cardiac vascular resistance, as well as systemic metabolic effects. A direct arrhythmogenic effect could also contribute to fatal evolution. Additional to direct pathogenic effects, the prognostic value of catecholamines could be related to roles as indicators of disorders and hemodynamic states of the patient (39), and we have seen this with our own experience in tetanus (40). The degree of sympathetic activation is related to the magnitude of heart failure, and very high values of circulating catecholamines are related to cardiogenic shock. However, in patients with or without alteration of the left ventricular function, a broad spectrum of plasma catecholamine values is observed, showing perhaps an individual physiological diversity (41).

We were able to establish that the levels of NE in tetanic patients and those with GBS in baseline conditions, without a sympathetic hyperactivity crisis, are above the levels of blood donors and critically ill patients in general. This result suggests that these patients have a baseline state of increased sympathetic activity, even in moments of apparent cardiovascular stability. Blood HA levels showed no increase or significant differences between all groups. According to these findings and the dispersion of the values obtained, we consider it is not feasible to establish "normal levels" of these substances in the blood, even in the group of donors considered as the "healthy" control group. This observation coincides, as far as NE is concerned, with the observations made by Kopin (42) about the fact that a considerable portion of the NE formed is metabolized before reaching circulation. Furthermore, the one that reaches it gets levels that not only depend on the release rate of sympathetic nerve endings, but also local factors such as density, distribution, and amplitude of neuro-effector junctions, on the one hand, and purification and excretion factors of NE, among other.

HA situation is even more complicated since its determination is made not in plasma, but whole blood, so that the circulating pool is included, with "de novo" formation due to sympathetic neurostimulation, as to the cellular deposit pool. The rapid rate of plasma disappearance of HA makes its determination impossible in this compartment since free HA in the circulation is rapidly captured in cellular elements (43). However, HA related to nerve structures stored are not of mast cells origin, since compound 48/80, known as a compound that increases mast cell degranulation, does not reduce the concentration of HA in these nerve structures, and hence it can be discarded the influence of a mastocitary pool in our present results (44).

It is striking that the parameters of blood pressure and heart rate showed no significant difference between any of the groups studied. It could be explained because both critical and tetanus patients with GBS were subject to control treatment of their critical conditions so that a level of blood pressure and "normal" heart rate in them would reflect similar figures to that from the donor or healthy control group.

It should be noted that HA values followed those of NE under the conditions of high sympathetic activity (HSA) and low sympathetic activity (LSA) in which the critical patients were distributed. That is, patients with HSA, who showed significantly higher levels of NE than patients with LSA, also presented significantly higher levels of HA, which supports our hypothesis.

The correlation between the levels of HA and NE obtained in donor blood allows us to establish that there is no standard or expected blood levels, as we already mentioned, but that each person seems to have a level determined by their specific situation. Also, to speculate about the possibility that those who show high levels of NE and low levels of HA may be more susceptible to exaggerated sympathetic responses to stress. Alternatively, they belong to a group of people with the potential development of high blood pressure, as it has already postulated by Magaldi et al. (45), who demonstrated that in conditions of peripheral histamine deficiency induced by the irreversible inhibition of the enzyme histidine-decarboxylase with alpha-fluoro-methylhistidine results in sympathetic

facilitation, which is associated with arterial hypertension and tachycardia, suggesting the presence of inhibitory action of neuronal HA on the peripheral sympathetic nervous system. Neuronal histamine appears to be reflexly released, as an overall compensatory phenomenon, during enhanced sympathetic activity. Histamine may be inhibiting nor-adrenaline release from sympathetic nerve terminals, and thus vascular responses due to stress, via H_3 inhibitory receptors [18]. These results opened the possibility to establish the NE/HA ratio in people who show the condition of increased sympathetic activity, such as the so-called "essential hypertensive". In this respect, Campos et al. (20) showed that enhanced sympathetic activity due to treadmill exercise in normotensive humans is accompanied by a rise in blood histamine, while the rise in blood histamine does not occur in primary hypertensive humans during the same degree of physical exercise, suggesting that this interaction is faulty in such hypertensives and could be involved in the pathophysiology of the disease.

The correlation between both neurotransmitters levels in tetanus patients and those affected by GBS showed an inverse and significant correlation, which is consistent with the expected response that HA follows the NE during exaggerated sympathetic activation. The levels of NE in tetanic patients who developed sympathetic hyperactivity crises were more than double that of tetanus without a crisis. It is essential to highlight the fact that these levels were maintained even up to one hour after treatment with adrenergic blockers and having "clinically" controlled the crisis. This fact has to be taken into account by the implication of the persistence of high levels of catecholamines that accompany various pathologies whose treatment only consists of turning off the responses without acting more causally, which suggests that the facilitation of the release of NE persists, with the consequent deterioration of the organs or systems involved.

Under these conditions described, the role of the HA should be considered. In effect, it is known that HA is released in all types of shock. In low-output, high-resistance states, as in hypovolemic and cardiogenic shock. The prevailing view over the decades has been that HA is a noxious mediator contributing to the fatal outcome of shock. Nevertheless, as originally stated by Nagy (1990), HA effect contrary to previous notions, today it is known that its effect is beneficial, probably through the inhibition of excessive vasoconstriction and through a positive inotropic effect.

The fact that the peripheral modulation model of the sympathetic nervous system proposed by Campos is contralateral, and that it operates through a regulatory neuron that is activated by a peptidergic sensory afferent pathway (19), coincides with the concept of evolutionary organization of neuronal systems, in the sense that for the achievement of more significant discrimination the modulating response is established contralaterally (47). In this regard, Cajal, in his general theory of the interbreeding of the nerve pathways (48), points out that "At the level of the most developed species, the predominance of cross-roads is a strange fact that, rationally judging and although it was only for economic reasons, nature should have accepted the opposite provision", and further points out that "One thing is out of the question: the decussation was created first in the sensory pathways".

The presoreceptors act within the blood pressure levels of 160 and 60 mmHg, and this seems to be more the consequence of peripheral regulation factors than central control. Up to now, much has been known about the sympathetic vasoconstrictor effect. But we have little knowledge about the active vasodilation phenomenon that also operates in it (49,50).

The fact that hypoxemia was discarded in the sample of patients studied, it rules out the possibility of inducing sympathetic hyperactivity and its effect at the level of the local vascular tone that this factor could exert (51). Finally, we want to highlight the fact that the critical patients who presented renal insufficiency showed the highest histamine values obtained, corresponding to the extreme value (44.85 ng/mL) to a patient with a condition of chronic terminal renal insufficiency. This fact may be related to the urinary excretion of HA and its metabolites. However, it would be worth studying in greater detail, since some clinical events, such as generalized and intractable pruritus that chronic renal insufficiency patients usually present (52), could in this finding have an explanation, and a reasonable basis of treatment.

CONCLUSIONS

1. According to these findings and the dispersion of the values obtained, we consider it is not feasible to establish "normal levels" of NE and HA in the blood.
2. In patients suffering from tetanus and patients with GBS, there is a state of baseline sympathetic hyperactivity, even without clinically manifestation of hyperactivity crisis.
3. The arterial blood pressure and heart rate parameters, taken in isolation, do not reflect the underlying existence of the sympathetic hyperactivity condition.
4. It is confirmed the hypothesis that under physiological response conditions, blood histamine levels follow those of norepinephrine during sympathetic activation.
5. In basal conditions, there is a population with a tendency to high levels of blood NE which is associated with low levels of HA, in which the correlation with underlying pathologies requires further evaluation.
6. The sharp increase in the level of NE, which is not followed by an increase in HA levels during the sympathetic hyperactivity crisis must be taken into account as a possible factor to present this complication in tetanus affected patients.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

F.P. de M: Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work;

M.V: Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS STATEMENTS

Studies involving animal subjects. Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects. Generated Statement: The studies involving human participants were reviewed and approved by the Ethics Committee of the University Hospital of Caracas. The patients/participants provided their written informed consent to participate in this study.

INCLUSION OF IDENTIFIABLE HUMAN DATA. Generated Statement: No potentially identifiable human images or data are presented in this study.

DATA AVAILABILITY STATEMENT GENERATED STATEMENT. All data sets generated for this study are included in the manuscript/supplementary files.

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