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# Cardiovascular drugs in human mechanical nociception: digoxin, amlodipine, propranolol, pindolol and atenolol.

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**Key words:** Mechanical nociception, pain modulation, atenolol, pindolol, propranolol, digoxin, amlodipine.

**Abstract.** Calcium channel blockers, $\beta$ adrenergic receptor blockers and Na/K ATPase inhibitors are widely used drugs, mainly for cardiovascular diseases. Their pharmacological targets are not restricted to the cardivascular tissue, nociceptive system structures also express similar targets, which strongly suggests a direct effect on pain sensation. To evaluate the pain intensity changes in outpatient groups, who receive these drugs as a therapy, a cross-sectional sampled, randomized patient groups receiving the calcium channel blocker amlodipine for blood hypertension (n=45), $\beta$ adrenergic receptor blockers (propranolol, atenolol or pindolol; n=40) for blood hypertension, or digoxin (n=40) for heart failure, were compared to an aparently healthy volunteers control group (n=60). A calibrated noxious pressure of 890 g/mm$^2$ was applied for 5 seconds on the patient's sternum. Subjective pain intensity was reported by the visual analog scale (VAS, 0 to 10). Pain modulation system was evaluated by the application of a second stimulus with a 5 minutes delay. The analgesic effect of the $\beta$ blockers group (propanolol, atenolol, pindolol) was dosage-dependant (–36.8%; P=0.0000003), without differences among them. The calcium channel blocker amlodipine showed lower pain scores (–50.6%; P=0.0000003) than $\beta$-receptor blockers (P=0.0000003). Digoxin presented the highest pain scores (+56.5%; P=0.0000003). All pain scores for the second stimulus were lower than the first stimulus and were differentially affected by $\beta$-blockers (atenolol, pindolol and propanolol) and calcium channel blocker (amlodipine), but not by digoxin. These results suggest the influence of widely clinically used cardiovascular drugs on nociception.

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**Medicamentos cardiovasculares en la nocicepción mecánica humana: digoxina, amlodipina, propranolol, pindolol y atenolol.**
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**Palabras clave:** Nocicepción mecánica, modulación del dolor, atenolol, pindolol, propranolol, digoxina, amlodipina.

**Resumen.** Los bloqueadores de los canales de calcio, los bloqueadores de los receptores $\beta$ adrenérgicos y los inhibidores de la ATPasa Na/K son medicamentos ampliamente usados en enfermedades cardiovasculares. Sus blancos farmacológicos no se restringen al tejido cardiovascular, el sistema nervioso nociceptivo expresa blancos similares, lo que sugiere fuertemente un efecto directo en la sensación del dolor. El objetivo del presente estudio fue evaluar los cambios en la intensidad del dolor en grupos de pacientes ambulatorios que reciban estos medicamentos como terapia. Grupos aleatorios de pacientes que reciben el bloqueador de canales de calcio amlodipina contra la hipertensión arterial (n=45), bloqueadores de receptores $\beta$ adrenérgicos (propranolol, atenolol or pindolol; n=40) contra la hipertensión arterial o digoxina (n=40) por insuficiencia cardíaca fueron comparados con un grupo control de voluntarios aparentemente sanos (n=60). A todos los grupos se les aplicó una presión nociva calibrada de 890 g/mm$^2$ durante 5 segundos sobre el esternón. El paciente reportó la intensidad subjetiva del dolor mediante la escala visual análoga (VAS). El sistema de modulación descendente del dolor fue evaluado mediante la aplicación del mismo estímulo 5 minutos después del primero. Se determinó un efecto analgésico en el grupo de $\beta$ bloqueantes (propanolol, atenolol, pindolol) dosis dependiente (–36,8%; P=0,0000003) sin mostrar diferencias entre ellos. El bloqueador de canales de calcio amlodipina mostró un efecto analgésico (–50,6%; P=0,0000003) que fue mayor que el de los $\beta$ bloqueantes (P=0,0000003). El grupo con digoxina expresó un efecto hiperalgésico (+56,5%; P=0,0000003). Todos los valores de dolor para el segundo estímulo fueron menores que para el primero y fueron diferencialmente afectados por los $\beta$ bloqueantes (atenolol, pindolol and propanolol) y por la amlodipina pero no por la digoxina. Estos resultados claramente sugieren la intensa influencia en la nocicepción de los ampliamente usados medicamentos cardiovasculares.

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## INTRODUCTION

Calcium channel blockers, $\beta$ adrenergic receptors blockers, and Na/K ATPase inhibitors are widely administered for hypertension, arrhythmia or heart failure, respectively. Neuronal membranes of nociceptive system structures express similar receptors (1), channels (2-5) and ionic pumps (6-8), suggesting potential effects on clinical nociception.

Neurotransmitter release involved in nociception depends on the activation of voltage sensitive calcium channels (2, 4, 9).

Calcium channels blockers show anti-nociceptive effects in both, experimental (4, 5) and clinical studies (3), but can also abolish opioid-induced hypersensitivity (10).

The $\beta$-adrenergic blockers have a stabilization action on the cellular membranes (11). Propranolol shows a local anesthetic effect similar to lidocaine by decreasing sodium (12) and calcium influxes (13).

During noxious stimulation, nociceptive neurons increase ATPase activity as a countermeasure to sodium influx (14). Acute peripheral inflammation increases not only Na/K-ATPase, but also Na-ATPase and fluoride-resistant acid phosphatase (FRAP) in the ipsilateral spinal dorsal horn, to restore the $Na^+$ and $K^+$ gradients associated to continued neuronal discharges (14,15) and to reduce the glutamate release (6). These two factors are strongly associated with hyperalgesia and allodynia (7). Digoxin, a Na/K ATPase inhibitor, increases the intracellular concentration of sodium and calcium (16) inducing neuronal depolarization (16), which antagonizes the antinociceptive effect of morphine in mice (17).

It has been proposed that a noxious stimulus can activate various antinociceptive mechanisms, such as diffuse nociceptive inhibitory control (DNIC) (18), propriospinal antinociceptive responses (19) and descending modulatory system (20); however, the action of calcium channels blockers, $\beta$-adrenergic blockers and digoxin on these antinociceptive mechanisms has not been extensively analysed.

Despite of a profuse study of basic mechanisms of action of these drugs *vide supra,* less attention has been paid to acquired pain sensation changes induced in patients taking calcium channels blockers, $\beta$ adrenergic blockers or ATPase inhibitors therapeutically for cardiovascular diseases and not for pain treatment.

## METHODS

The experimental protocol was approved by the Área de Estudios de Postgrado of the Universidad de Carabobo and the Hospital Research Committee of the Social Security Hospital "Dr. Angel Larralde". Informed consent was obtained from patients and volunteers.

### Patients

The cross-sectional, randomized sample consisted of patients from the outpatient Internal Medicine Service and by, apparently, healthy volunteers, workers of the same Hospital area. The subjects were grouped according to their drug therapy as follows: $\beta$ receptors blockers group: with $\beta$-blockers treatment, distributed in three subgroups i.e., atenolol, pindolol or propranolol; calcium channels blockers group: with amlodipine; ATPase inhibitor group: with digoxin. Due to the nature of the study, internal controls (pain scores before and after the drug intake) were not possible, hence, a control group was included with apparently healthy, asymptomatic, volunteers without any pharmacological treatment. An interview was performed to confirm their health status.

Subjects included were older than 20 years, of both sexes, who received monotherapy either with $\beta$-blockers atenolol, pindolol or propanolol, calcium channel blocker (amlodipine) or cardiac glycoside (digoxin), for more than 6 months and clinically stable. Those patients who had received analgesic drugs 72 hours previous to the study, drank caffeine or smoked tobacco two hours before the test, or those patients with pathologies that affected their sensitive, cognitive, or discriminative capabilities, or those that received pharmacological polytherapy, or those clinically uncompensated, were excluded from the study.

**Treatment and measurements**

Data were obtained from the clinical history, physical examination, recording of drug dose and values of the Visual Analogical Scale VAS to a calibrated noxious mechanical test. Drugs were administrated in daily oral doses as follows: amlodipine 2.5-10 mg, propranolol 20-600mg, atenolol 25-100 mg, pindolol 5 mg and digoxin 250 $\mu$g.

In the outpatient room, a constant noxious pressure gauged to 890 g.mm$^{-2}$ generated by a 2 mm$^2$ flat tip spring device was applied for 5 seconds on the sternum's Louis angle of the patient, this midline body location for the stimulus was selected to avoid individual asymmetries in pain sensation (14). The noxious pressure did not induce lesions in the skin. The patient used a vertical Visual Analog Scale $VAS_1$, a self reported subjective pain intensity scale. After 5 minutes of resting time, the same stimuli was applied again to evaluate the pain modulation systems, this interval of time was used due to the reported short lasting antinociceptive effects of the first (conditioning) noxious stimulus (18).

**Statistics**

Values were presented as arithmetic means ± standard deviations. Distribution of the data was analyzed by the Kolmogorov-Smirnov test. The percentage of difference of VAS values between groups was evaluated by the non parametric Wilcoxon test. Linear regression analysis was performed. Significance level was set at $P<0.01$.

## RESULTS

The study was realized in a total sample of 185 subjects (Table I). Sixty asymptomatic, apparently healthy subjects were included in the control group. The mean age was 48.29 ± 17.86 years (range 21-86 years), 51.35% of the subjects were male. Arterial hypertension (AH) was present as the sole illness in 85 (68%) patients, which showed blood pressure of 85.2 ± 3.2 mmHg and 122.4 ± 4.1 mmHg for diastolic and systolic values respectively, not statistically different to those from the control group ($P>0.1$). Heart failure (HF) was present in 40 (32%) patients which received digoxin as treatment. The primary cause of HF of this group was arterial hypertension. No age or sex distribution differences were found between control, $\beta$-blockers and amlodipine groups ($P=0.1$). Digoxin group showed higher mean age than the other groups ($P=0.0001$; Table I).

Patients in the $\beta$-blockers group (n=45; Table II) were distributed according to the drug as follows: atenolol (n=25; 55.6%), pindolol (n=7; 15.6%) and propranolol (n=13; 28.9%). Patients with arterial hypertension showed more than 42% reduction on VAS values when compared with the control group values

**TABLE I**
SAMPLE SIZE, AGE, RANGE AND STATISTICAL COMPARISON AMONG DIFFERENT PATIENT AND CONTROL GROUPS

| Group | n | Age (years) | Range | P |
|---|---|---|---|---|
| Control | 60 | 43.34 ± 15.22 | 21-84 | |
| $\beta$-blockers | 45 | 44.11 ± 12.23 | 24-79 | ns |
| Amlodipine | 40 | 47.23 ± 11.66 | 28-73 | ns |
| Digoxin | 70 | 35 ± 7.03 | 45-86 | ** |

X ± SD. **P<0.0000001. ns: P>0.01 (against Control).

(Table III) but, patients with heart failure and digoxin treatment showed more than 57% increase on VAS values compared with the control group. HF in patients with AH switches the VAS values from low (negative %) to high pain scores (positive %) from 174 to 212% (Table III).

These three subgroups did not show statistical differences (P=0.13) in age, sex or VAS values distribution, thus, they were grouped together (Table IV).

When comparing the VAS values between the different groups in the $\beta$-blockers group presented a 36.8% (P=0.0000001) reduction in the reported pain intensity when comparing with the control group; the reduction percentage was even higher for the amlodipine group being 50.6%

**TABLE II**
PATIENT DISTRIBUTION IN THE $\beta$-BLOCKERS GROUP ACCORDING TO THE DRUG AND COMPARISON BETWEEN THEIR VAS VALUES

| | Propranolol | Atenolol | Pindolol | P |
|---|---|---|---|---|
| n | 13 | 25 | 7 | |
| $VAS_1$ | 3.57 ± 0.80 | 3.45 ± 1.00 | 3.94 ± 1.11 | >0.27 |
| $VAS_2$ | 2.92 ± 0.92 | 2.88 ± 0.86 | 3.50 ± 1.26 | >0.13 |

VAS values are X±SD; P is the best value of all pair tests from the three groups.

**TABLE III**
DISTRIBUTION AND VAS VALUES OF CONTROL SUBJECTS, PATIENTS WITH ARTERIAL HYPERTENSION OR ARTERIAL HYPERTENSION INDUCED HEART FAILURE

| Patients | n | $VAS_1$ | % | $VAS_2$ | % |
|---|---|---|---|---|---|
| Controls | 60 | 5.64 ± 1.50 | –42.55 | 5.21 ± 1.44 | –49.32 |
| AH | 85 | 3.24 ± 1.05** | +57.44 | 2.64 ± 1.07** | +58.54 |
| AH + HF | 40 | 8.88 ± 1.27** | +174.07** | 8.26 ± 1.13** | +212.88* |

AH: arterial hypertension (n=85). HF: heart failure (n=40). Values are X ± SD.
*P<0.001. **P<0.0000001. Last row of % is the differences between AH+HF group and AH group.

**TABLE IV**
VAS VALUES, ANALGESIC INDEX, PERCENTAGE OF CHANGE AND T-TEST FOR THE STUDIED GROUPS

| | Control | $\beta$-blockers | Amlodipine | Digoxin |
|---|---|---|---|---|
| n | 60 | 45 | 40 | 40 |
| $VAS_1$ | 5.63 ± 1.49 | 3.56 ± 0.95 | 2.78 ± 0.92 | 8.81 ± 0.92 |
| Δgroup (%) | | –36.8** | –50.6** | +56.5** |
| $VAS_2$ | 5.17 ± 1.45 | 2.98 ± 0.94 | 2.18 ± 1.00 | 8.19 ± 1.21 |
| Δgroup (%) | | –42.4** | –57.8** | +58.4** |
| $\Delta VAS_{1\text{-}2}$ (%) | –6.13* | –16.28** | –23.78** | –6.93 (ns) |

VAS values are X±SD. All reported P values are control group comparison. Δgroup (%) are differences between that particular VAS group value against the control group (100%), negative values means analgesia and positive values means hyperalgesia. For $\Delta VAS_{1\text{-}2}$, $VAS_1$ was considered 100%.
*P=0.0003. **P=0.0000001. ns=P<0.01.

(P=0.0000001) lower than the control group. In contrast, the digoxin group showed and increment up to +56.5% (P=0.0000001) when comparing the VAS values with the control group. The group of patients who received amlodipine showed the strongest reduction of pain intensity values for the mechanical noxious stimulation with –50.6% and –57.8%; P<0.0000001 for $VAS_1$ and $VAS_2$ respectively (Table IV), less than the control group. The highest differences in pain scores respect to control values were observed in patients who received digoxin showing +56.5% and +58.4% for $VAS_1$ and $VAS_2$ respectively, higher than the values reported for the control group (P<0.0000001).

The linear regression for the administered dosage of $\beta$-blockers and VAS values revealed dose-dependent effects for atenolol (n=25; $VAS_1$ $r$ = –0.69; P=0.00012; $VAS_2$ $r$ = –0.61; P=0.0013), but not for propranolol (n=13; $VAS_1$ $r$ = –0.46; P = 0.12; $VAS_2$ $r$ = –0.31; p = 0.30). No regression analysis was made for pindolol due to the use of only 5 mg dose schedule. The administered dosage of amlodipine was associated inversely to $VAS_1$ (n = 40; $r$ = –0.43; P=0.005) and $VAS_2$ values (n = 40; $r$ = –0.42; P=0.0074). No regression analysis was made for digoxin due to the use of only 0.25 mg dose schedule. The duration of the treatment was not related to VAS values for the $\beta$-blockers ($r$ = 0.18; P = 0.24), amlodipine ($r$ = 0.042; p = 0.80) as well as for the digoxin group ($r$ = 0.22; P = 0.17).

$VAS_2$ values were lower than those of $VAS_1$ for all groups except for the group who received digoxin. The ranking of pain intensity reduction in VAS scores (ΔVAS) was Control < $\beta$-blockers (propranolol, atenolol, pindolol) < calcium blocker (amlodipine) with –6.13%; –16.28% and –23.78% respectively (Table IV). Additionally, ΔVAS values for $\beta$-blockers and amlodipine patient groups were statistically more intense than for the control group (P<0.01).

## DISCUSSION

The present cross-sectional study evaluated the effect of the therapy of cardiovascular diseases, such as arterial hypertension and/or heart failure with $\beta$-blockers, calcium channel blocker or cardiac glycoside on mechanical nociception in 125 patients, compared to 60 healthy volunteers without medication.

It is known that arterial hypertension is associated to hypoalgesia in animals (22, 23) and humans (24). In the present study, the patient group undergoing $\beta$-blockers therapy, according to the inclusion criteria, were clinically stable with diastolic and systolic blood pressure values ≤85mmHg and ≤123mmHg respectively. There is strong evidence that blood pressure correlates positively with pain thresholds and negatively with pain ratings (23) thus, the lower pain scores respect to control values observed in patients with $\beta$-blockers therapy, could not be explained only by the arterial hypertension because their blood pressure values were not different than those of the control group. The results suggest that the three $\beta$-blockers tested play a direct effect for lowering pain scores. The dose-effect correlation observed in the atenolol, but not in propranolol patient group, could be explained by $\beta_1$ selectivity, blood-brain barrier impermeability and less membrane stabilizing effect for atenolol. The current study confirms previous findings about the role of $\beta$-adrenergic receptors in nociception (12, 13), based on decrease of the adenylcyclase activity (25), reduction of intracellular AMPc and inhibition of voltage sensitive calcium and sodium channels activity (12, 13, 26), which lead to a decrease of neuronal excitability. Additionally, $\beta$-blockers are able to suppress IL-6 (27) and TNF$\alpha$ (28)

release and to inhibit the phospholipase A (29), all these actions are strongly linked to analgesia (7).

Like the results from patients with $\beta$-blockers therapy, neither systolic nor diastolic blood pressure from patients with amlodipine therapy was different to those from the control group. Thus, the possible contribution of blood pressure values to reduce pain sensation should be marginal *vide supra*. The analgesic effect observed in patients receiving amlodipine agrees with previous reports, that support the notion that voltage sensitive calcium channel blockers decrease neuronal excitability, by means of reducing calcium influx by a dose-response effect (30). Neurons with a wide variety of calcium channels in their cellular membrane have been described in nociceptive pathways and centers (31), playing an important role for sensitization and potentiation of nociceptive neurons and their neuronal network (8, 9). The clinical results of the present study confirms previous findings about the relevant role of voltage sensitive calcium channels in human nociception (3, 7, 31).

The group of patients with digoxin therapy shows the higher values of subjective intensity to mechanical noxious stimulus. The digoxin-induced inhibition of the Na/K ATPase, not only in the heart, but also in neurons, leads to an increase of the intracellular sodium concentrations, which depolarizes the neuron, increases their excitability (6, 14, 16) and opens voltage sensitive calcium and sodium channels with a strong neuronal depolarization (7). Neuronal depolarization and release of excitatory amino acid are mimicked by ouabain (32). Consistently, well known analgesic substances like morphine and encephaline analogues significantly increase Na/K ATPase activity; on the other hand, the opiate antagonist, naloxone, decreased the activity of Na/K ATPase (33). However, the effect of ouabain is not completely clear. Spinal intrathecally administered ouabain has been reported to produce antinociception via an enhancement of cholinergic transmission in the spinal nociceptive processing system (34), but intracerebroventricular application of ouabain antagonizes opioid analgesia, which suggests its effect on supraspinal Na/K-ATPase (17).

It is well known that blood levels of interleukins IL-6 and TNF$\alpha$ rise in patients with heart failure showing a direct correlation between their blood concentration and the heart failure grade (35). These products exert a clear proinflammatory and proalgesic effects (36) which could contribute to the increased subjective pain intensity rates of the digoxin/heart failure patient group; however, this group, were all clinically stable, condition associated to low increases of blood concentrations of IL-6 and TNF$\alpha$ (37, 38). Moreover, the age related increase of these cytocines was reported particularly in patients over 85 years of age (39). The age of the digoxin patient group evaluated in the present study was 15 years younger, but the role of age related increase of cytocines cannot be ruled out, together with the ATPase inhibition induced by digoxin to explain the increased subjetive pain intensity reported by the patient group. However, since cytokines levels were not measured in the current study, the influence of cytokines in the digoxin/heart failure patient group can not be proven.

Circulating Na, K-ATPase inhibitory and digoxin-like immunoreactivity factors have been reported increased in patients with heart failure (40, 41), but once again, the clinically stable status for the digoxin/heart failure patient group, strongly suggests that the main contribution for the hyperalgesia is made by digoxin. However, it cannot completely ruled out that patients receiving digoxin were age and co-morbidity

different to the control group. The cross-sectional design of the study raises some limitations about homogeneity between the control and digoxin groups.

The group receiving amlodipine showed a higher analgesic effect than the $\beta$-blockers therapy group, i.e., propranolol, atenolol or pindolol, which suggests a greater effect of the calcium ion and its voltage sensitive channels over the stabilizing membrane effect produced by the $\beta$-adrenergic receptor blockers for mechanical noxious stimulation.

The significant reduction of $VAS_2$ over $VAS_1$ values ranged between –7% to –21% observed at least 5 minutes after the first (conditioning) noxious stimulation which agrees with pain modulation system activation (42, 43), was differentially affected by the voltage sensitive calcium channel blocker amlodipine, $\beta$-adrenergic receptor blockers, i.e., propranolol, atenolol and pindolol, but not by the ATPase inhibitor digoxin, these different pharmacological responses confirms that in pain modulation systems, which includes spinal and supra-spinal mechanisms, both calcium channels and $\beta$-adrenergic receptors blockers play a fundamental role with a major effect of the calcium channels as shown intra and intergroup $\Delta$VAS values of the present study, with no influence of the treatment time.

Despite that results confirm and agree with previous basic and clinical findings, the cross sectional experimental design and the use of healthy volunteers as a control group, that make possible the present study, also generate difficulties in the interpretation of the results because it is no possible to determine whether the found changes in nociception are due to the treatment or to the underlying pathology of the subjects.

Arterial hypertension and heart failure are common morbility that affects at least 20% of the population. The present study suggests the influence on nociception of widely used drugs in these cardiovascular diseases, showing that calcium channel and $\beta$-adrenergic receptors blockers, could decrease and digoxin could increase pain sensation. The clinical possibility to use both mechanisms, such as a synergic antinociceptive action must be further tested, based on the advantage of current available calcium channel and adrenergic receptors blockers, but careful analysis of the effects on cardiovascular parameters like blood pressure are needed.

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