

## Anti-Hypertensive Treatments and Hypertension-Associated Hypoalgesia Evaluated by Auto-Algometry

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### Abstract

**Background:** Auto-algometry has been previously proposed as a tool to evaluate hypertension-associated hypoalgesia. The aim of the present work was to confirm the robustness of this method and to evaluate other possible variables associated with hypertension and hypoalgesia.

**Methods:** All routine ambulatory data were collected from 111 hypertensive subjects along with the evaluation of pain threshold assessed with the auto-algometer.

**Results:** The results confirmed the sensibility of the auto-algometer in revealing the hypertension-associated hypoalgesia and revealed unexpected higher pain thresholds in patients consuming angiotensin receptor 1 antagonists compared to patients consuming other medications.

**Conclusion:** The results encourage the use of the auto-algometer to study unexplored mechanisms involved in hypertension and in hypoalgesia.

**Keywords:** Auto-algometry; Hypertension-associated hypoalgesia; Pain threshold; Angiotensin receptor 1 antagonists

### Introduction

It has long been described that essential hypertension is associated with a sort of hypoalgesia [1-3]. In a previous work, our group have described the use of a novel low-cost computerized auto-algometer that is able to reveal such hypertension-associated hypoalgesia and is very easy to use in hypertension ambulatory routine [4]; this method essentially consists of producing an acute, and very transient, puncture-type pain, while measuring the force applied to the needle used to produce such pain, with the peculiarity that it is the subject under evaluation that applies to himself such painful stimulus by pushing his fingers against the needle. The aim of the present work was to collect routine ambulatory data along with the pain threshold determined with the auto-algometer on a large sample of hypertensive subjects, to further confirm the robustness of this method and to evaluate other possible variables associated with hypertension and hypoalgesia.

### Methods

111 hypertensive patients were enrolled at the Ambulatory for Hypertension of the Faculty of Medicine of the Second University of Naples (Table 1). Potential participants were screened among patients coming for regular follow-up to determine if they met the following inclusion criteria: essential hypertension diagnosed since 3 years at least; continued treatment with one of the following: angiotensin-converting enzyme-inhibitors: enalapril 20 mg or ramipril 5 mg; angiotensin II type 1 receptor antagonists: losartan 50-100 mg or olmesartan 20-40 mg; beta-blockers: bisoprolol 2.5-5 mg; calcium-antagonists: amlodipine 5-10 mg or barnidipine 10-20 mg. Patients with obesity, diabetes, peripheral neuropathy, chronic pain, cardiac or pulmonary disease, and/or history of stroke or neuropsychiatric disturbances were excluded. The intactness of sensation and of peripheral nervous system was assessed by a general neurological exam and somatosensory tests (monofilament test, tuning fork test, warm-cold water test). All procedures conform to the directives of the Declaration of Helsinki, adhere to Good Clinical Practice guidelines as outlined by the International Conference on Harmonisation and were approved by the local ethical committee of the Second University of Naples; all patients gave their informed consent to participate to the study.

	Women	Men
n	52	59
Age (Years ± S.E.)	62.5 ± 1.4	61.5 ± 1.4
Weight (Kg ± S.E.)	72.0 ± 1.8	84.0 ± 1.5
Height (cm ± S.E.)	155 ± 0.8	170 ± 0.9

**Table 1:** Main demographic data of the hypertensive patients participating to the study.

All patients were under pharmacological treatment for essential hypertension and had well controlled values for blood pressure; the ambulatory data collected for each patient were: age, sex, weight, height, body mass index, current systolic and diastolic blood pressure, days from last menstruation, age at the first time of hypertension diagnosis, current kind of anti-hypertensive drug therapy, presence of diabetes, smoking, heart valves diseases, cardiac ischemic disease, atheromatous plaques, other pathologies, other drugs intake.

A group of 34 normotensive subjects (systolic/diastolic=130 ± 10/80 ± 10 mm Hg, age 61 ± 3 y) was recruited among teaching and administrative personnel of the Second University of Naples, respecting the same exclusion criteria as previously mentioned. All subjects were Caucasian and come from the territory of Campania (Italy).

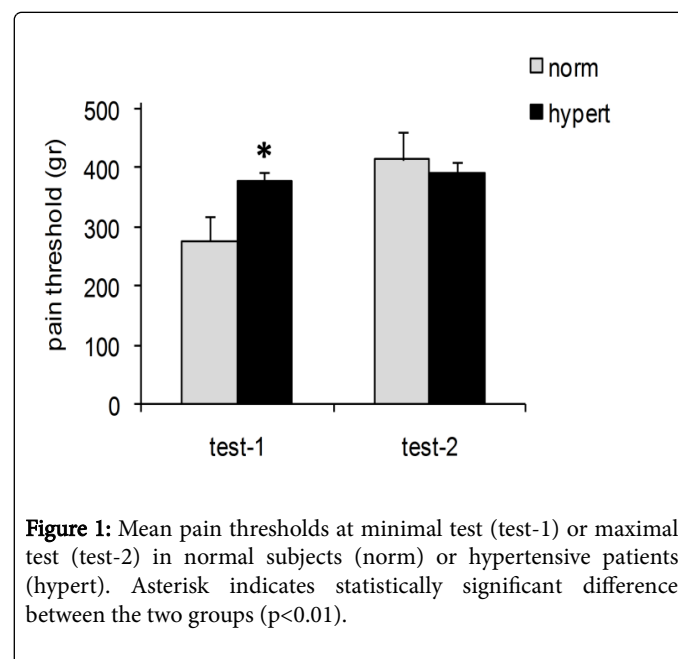
A computerized auto-algometer was used as previously described [4], with minor modifications; briefly, the instrument consisted of a needle with a 1 mm round tip, fixed in a vertical position to a load cell; the signal from the sensor was amplified through an instrumental amplifier (INA 125, Burr Brown, Dallas, TX, USA) and digitized with an A/D converter (Arduino, Robot Italy, Rome, Italy) connected to the USB port of a netbook; a custom software recorded the force applied on the needle. Subjects were asked to push down on the needle with the tip or the dorsal surface of their second, third, fourth and fifth finger (i.e. eight trials in total) until a minimal or a maximal pain sensation was evoked (i.e. the eight trials were repeated two times). Each subject performed all trials in one occasion; all the data for the present report were collected within one month. For each trial the maximal pressure applied by the subject was identified; then, the mean values of the eight minimal-trials (test-1) or the eight maximal-trials (test-2) were evaluated for each subject. The evaluation of the mean value over these eight trials was necessary for a more reliable evaluation of the pain threshold despite an inescapable variability of the measure, likely due to a blunted range of pain sensation; in fact, despite there is also an overlap among the values for test-1 and test-2 from all the subjects, for each subject the value for test-1 was always smaller than that for the test-2, as expected.

Data are presented as means ± standard error of the means. Linear regression analyses were used to evaluate possible correlations between numeric variables; Student's t-test was used to evaluate different values for numeric variables between two groups; the analysis of the variance (ANOVA) was used to evaluate different values for numeric variables with more than two groups. The pain thresholds obtained from the hypertensive subjects was compared with that obtained from a group of 34 age-matched normotensive subjects; despite a "white coat" anxiety effect could not be excluded in the present procedure, both hypertensive and normal subjects underwent the tests under the same

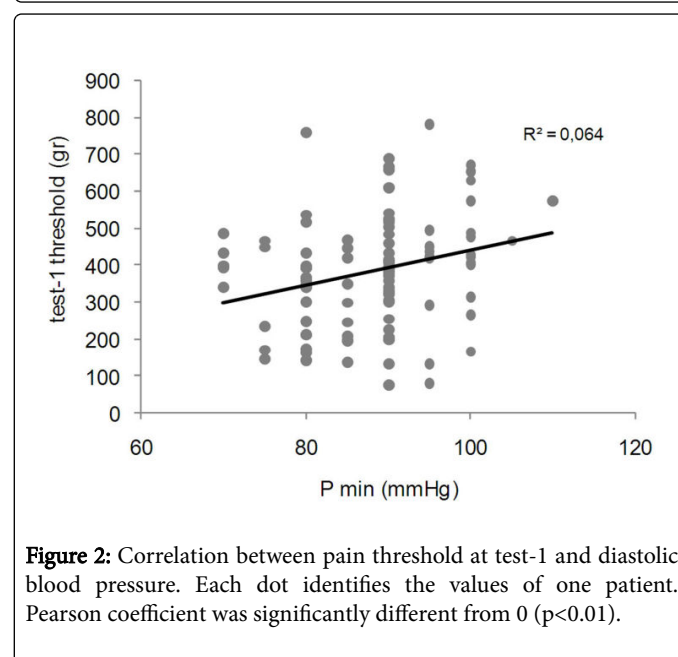
conditions, validating the comparison of their pain thresholds to reveal the effect of hypertension.

## Results

The mean pain thresholds for hypertensive patients determined with the auto-algometer in the present study were 379 ± 14 gr for test-1, and 393 ± 17 gr for test-2 (Figure 1); only the values for test-1 were significantly higher than those obtained from normotensive subjects (278 ± 41 gr for the minimal test, 415 ± 46 gr for the maximal test).



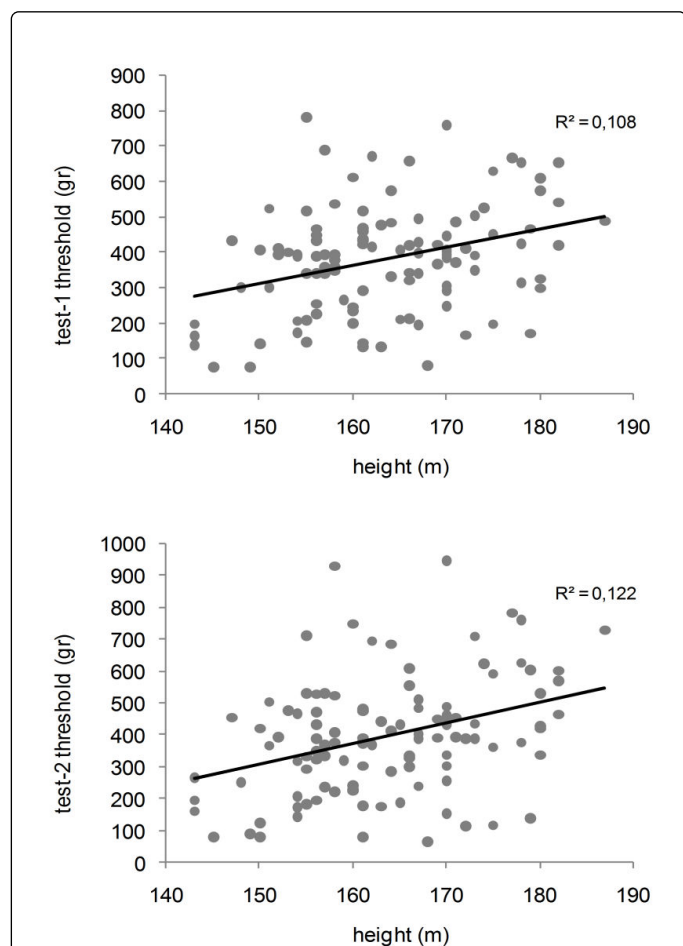
**Figure 1:** Mean pain thresholds at minimal test (test-1) or maximal test (test-2) in normal subjects (norm) or hypertensive patients (hypert). Asterisk indicates statistically significant difference between the two groups (p<0.01).



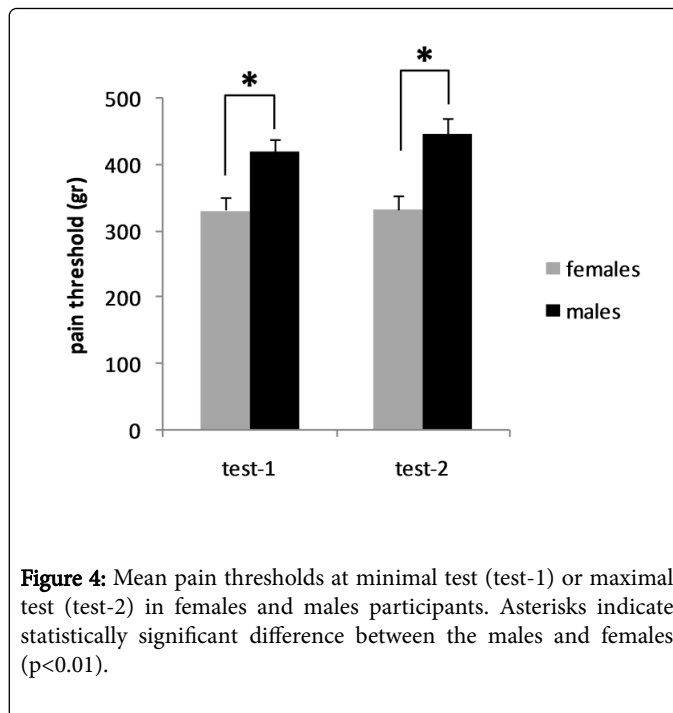
**Figure 2:** Correlation between pain threshold at test-1 and diastolic blood pressure. Each dot identifies the values of one patient. Pearson coefficient was significantly different from 0 (p<0.01).

A two-way ANOVA, being the first factor "hypertension" (two levels: with or without hypertension) and with repeated measures on the factor "test" (test-1 or test-2), showed a significant effect for the

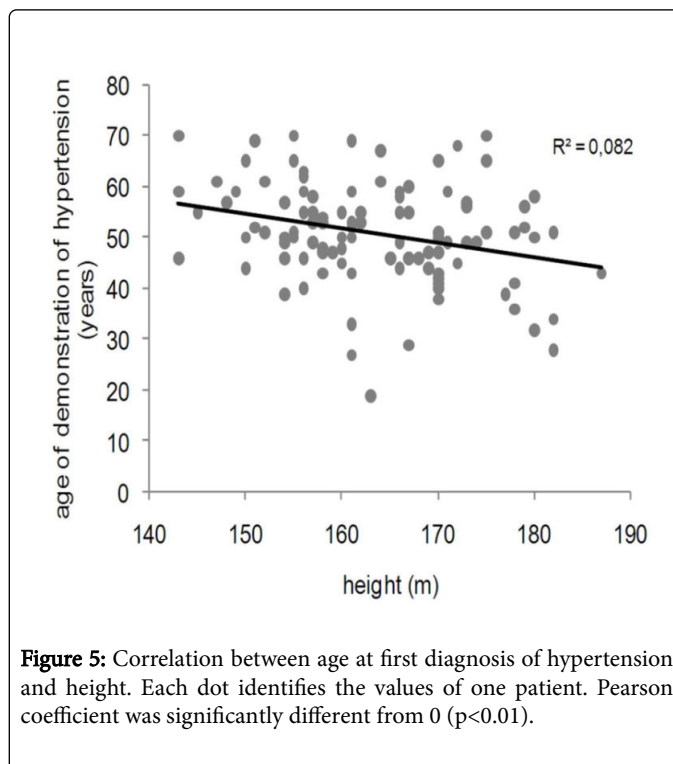
hypertension x test interaction ( $F_{1, 130}=36$ ;  $p<0.01$ ). Moreover, there was a positive correlation between the pain threshold at test-1 and the diastolic blood pressure of hypertensive patients ( $R^2=0.064$ ;  $p<0.01$ ; Figure 2); no significant correlations were seen between test-2 and diastolic blood pressure, or between test-1 or test-2 and systolic blood pressure. There was a positive correlation between patients' height and the thresholds determined with the auto-algometer in both the test-1 ( $R^2=0.108$ ;  $p<0.01$ ; Figure 3A) and the test-2 ( $R^2=0.122$ ;  $p<0.01$ ; Figure 3B); these correlations were not significant if evaluated in women or in men alone. There was a significant difference between female and male patients for the mean height ( $155 \pm 0.8$  cm vs.  $170 \pm 0.9$  cm;  $P<0.01$ ), and for both the test-1 and the test -2 threshold, with a lower threshold for females than for males (Figure 4). Conversely, considering the height as a covariate and correcting the pain threshold values for the height, the difference in pain threshold between women and men was not significant. There was also an inverse correlation between the height and the age at which hypertension was demonstrated for each patient ( $R^2=0.082$ ;  $P<0.01$ ; Figure 5).



**Figure 3:** Correlation between pain threshold at test-1 (panel A) or test-2 (panel B) and height. Each dot identifies the values of one patient. Pearson coefficients were significantly different from 0 in both cases ( $P<0.01$ ).

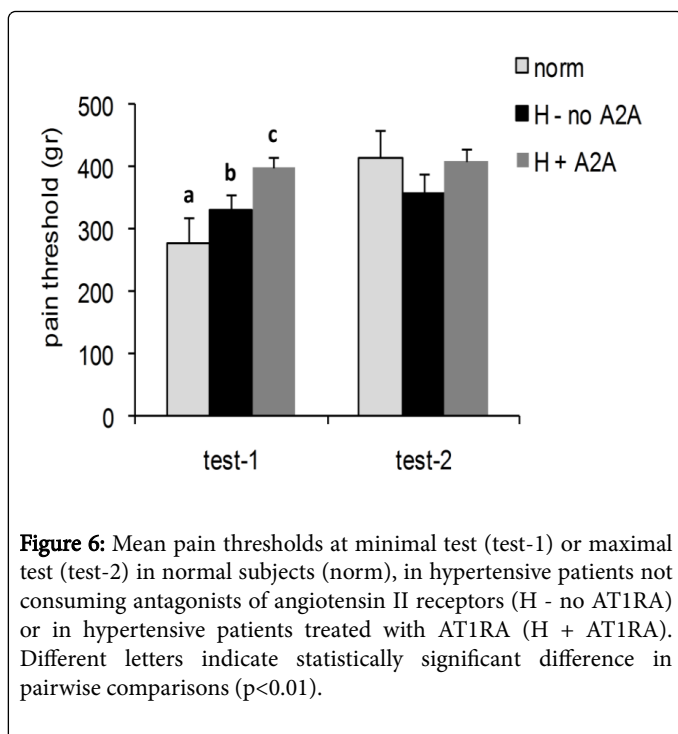


**Figure 4:** Mean pain thresholds at minimal test (test-1) or maximal test (test-2) in females and males participants. Asterisks indicate statistically significant difference between the males and females ( $p<0.01$ ).



**Figure 5:** Correlation between age at first diagnosis of hypertension and height. Each dot identifies the values of one patient. Pearson coefficient was significantly different from 0 ( $p<0.01$ ).

In test-1, the pain threshold of patients consuming angiotensin II type 1 receptor antagonists. (AT1RA,  $n=78$ ) was higher than in other patients ( $n=33$ ). A two-way ANOVA, with factor treatment (3 levels: no hypertension, hypertension without intake of AT1RA, hypertension plus intake of AT1RA) and repeated measures on factor test (minimal test or maximal test), showed a significant effect for the treatment x test interaction ( $F_{2, 129}=18.3$ ;  $p<0.01$ ; Figure 6).



**Figure 6:** Mean pain thresholds at minimal test (test-1) or maximal test (test-2) in normal subjects (norm), in hypertensive patients not consuming antagonists of angiotensin II receptors (H - no AT1RA) or in hypertensive patients treated with AT1RA (H + AT1RA). Different letters indicate statistically significant difference in pairwise comparisons ( $p < 0.01$ ).

The difference between patients consuming AT1RA and patients not consuming AT1RA was also significant on a t-test with data corrected for the intake of all other drugs except ACE inhibitors ( $p < 0.05$ ), while this difference was not significant on t-tests with data corrected for the use of ACE inhibitors. The clinical profile, comprising all the variables listed in methods (age, sex, weight, height, body mass index, current systolic and diastolic blood pressure, days from last menstruation, age at the first time of hypertension diagnosis, current kind of anti-hypertensive drug therapy, presence of diabetes, smoking, heart valves diseases, cardiac ischemic disease, atheromatous plaques, other pathologies, other drugs intake) did not differ between patients taking different medications.

## Discussion

The present study confirms on a large sample of hypertensive patients that the auto-algometer previously described [4] is a valuable tool to reveal the hypoalgesia associated with hypertension. In particular, it has been demonstrated that the threshold for the minimal pain sensation (test-1), but not that for the maximal pain sensation (test-2), is significantly higher in hypertensive patients than in normal subjects (Figure 1). This is an important methodological aspect to take into account when studying hypertension-associated hypoalgesia. The positive correlation between test-1 and diastolic blood pressure (Figure 2), along with the lack of correlation with systolic blood pressure or between test-2 and blood pressure, further highlights the relevance of evaluating the minimal pain threshold and suggests that there is a common mechanism involved in hypoalgesia and in diastolic blood pressure. At present this mechanism is unknown, but, given that the diastolic blood pressure is mainly a consequence of peripheral vascular resistance, it can be argued that also the associated hypoalgesia could be a consequence of some factors involved in the regulation of vessel tone. Because the correlation had a small effect size, there may be other unknown explanatory variables that could explain this result. Numerous papers have confirmed the correlation between

hypertension and pain sensitivity for many years. Interestingly, animal models have shown a possible effect of angiotensin receptors in modulating pain perception [5-7], while it seems that a supraspinal modulation [8,9] and the opioid receptors [10] are unlikely involved in this phenomenon. Nevertheless, the involvement of the opioid system should be further studied; at least in male healthy volunteers, in fact, it has been shown that blockade of the opioid receptors abolishes the correlation between resting systolic blood pressure and subjective indices of pain rating [11].

The finding of a correlation between patients' height and pain threshold (Figure 3) was unexpected and it is difficult to explain, as there are no data in literature reporting this correlation. Because greater pain sensitivity for women has already been described in literature [12] and has been confirmed in the present study, it can be argued that it could be just a coincidence of phenomena with no cause-effect relation. Nevertheless, because the difference in pain threshold between women and men is not significant when the values of pain threshold are corrected with the values of height, and considering that even the mechanism for gender difference in pain threshold is not completely clear, future research should be conducted to evaluate which one between gender and height is the primary variable influencing pain threshold, or if there is, eventually, something else influencing pain threshold, height and sex.

The finding of an inverse correlation between patients' height and the age at which hypertension had been diagnosed (Figure 5) was again unexpected and difficult to explain, but considering that there is also a correlation between height and pain threshold (Figure 3), it can be argued that a common mechanism is related to height, pain threshold and blood pressure regulation.

In the present study it has been seen that patients consuming AT1RA had a greater hypoalgesia (Figure 6). It cannot be concluded whether this effect was due to the opposite effect of the use of ACE inhibitors, as the difference between patients consuming AT1RA and patients not consuming AT1RA was not significant with data corrected for the use of ACE inhibitors. Nevertheless, the finding of an effect of AT1RA on pain threshold has been already described in literature; in fact, in an animal model of type 2 diabetes it was seen that the treatment with an AT1RA induced hyperalgesia; moreover, in hypertensive patients it was seen that the treatment with ACE inhibitors or AT1RA resulted in a smaller hypoalgesia [3,13]. The apparent contrast with the finding of the present work is probably due to the different experimental model. In fact, in the present study the pain threshold of patients consuming AT1RA was compared with that of patients consuming other medications, while in both the works of Sugimoto et al. [14] or Guasti et al. [3,13] it was compared the pain threshold of a group of rats or patients before and after the treatment with ACE inhibitors or AT1RA, which, obviously, resulted also in an amelioration of blood pressure. Thus, the works of Guasti et al. [3,13], in particular, further suggest that there is a relation between blood pressure and pain threshold. It is noticeable that not only those subjects on ACEi or ARA, but also those on calcium antagonists may have their vascular tone altered; thus it can be argued that the mechanisms responsible for the effects on pain threshold of AT1RA do not involve only vascular tone and blood pressure. Angiotensin II, in fact, can modulate neuronal transmission within the central nervous system; type 1 receptors have been demonstrated in spinal cord, dorsal root ganglia and sciatic nerve of the rat [15]. Moreover, other works have shown that angiotensin II can play different roles in the modulation of pain transmission within the central nervous system; in

fact, it can have hyperalgesic effects when injected into the caudal ventrolateral medulla or intrathecal [16,17], or it can have hypoalgesic effects when injected into the periaqueductal grey or the rostral ventrolateral medulla [6,7,18,19]. Interestingly, an AT1RA can block the intrathecal-hyperalgesic effect of angiotensin II; moreover, it has also been shown that in mice the oral treatment with several ACE inhibitors or AT1RA resulted in hypoalgesia [7]. Overall, these data support a role for angiotensin II in the modulation of pain transmission and consequent possible effects of ACE inhibitors and AT1RA on pain threshold, but the exact mechanism is still unclear and needs further studies, particularly with further distinction on anti-hypertensive drugs; to this end, the auto-algometry methodology can be proposed as a valuable tool to use for future studies, because it is quantitative, objective and inexpensive.

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## Author Contributions

A. Viggiano invented and realized the auto-algometer. C. Aurilio, M.A. Tedesco and M. Giordano conceived the idea for the study. M.B. Passavanti, G. Zagaria, M.C. Pace, P. Sansone, S. Coaccioli and M.A. Tedesco collected data. R. Marfella, F. Esposito and M. Monda contributed to the analysis and interpretation of data.

All the authors discussed the results and revised and approved the final version of the manuscript.

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