

# Journal Pre-proof

[[Translated article]]Erythema, Localized Edema and Heat vs Forearm Perimeter Increase. Time to Revise the Consensus Recommendations on the Vortex Provocation Test in Vibratory Urticaria-Angioedema?

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Original

## Eritema, edema localizado y calor versus aumento del perímetro del antebrazo. ¿Ha llegado el momento de revisar las recomendaciones de consenso de la prueba de provocación del vórtice en urticaria-angioedema vibratorios

[[Translated article]]Erythema, Localized Edema and Heat vs Forearm Perimeter Increase. Time to Revise the Consensus Recommendations on the Vortex Provocation Test in Vibratory Urticaria-Angioedema?

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## Graphical abstract

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## Resumen

**Antecedentes:** En urticaria/angioedemas vibratorios se ha consensuado que la respuesta positiva al test de provocación del vórtice se defina en función del aumento del perímetro del antebrazo.

**Objetivo:** estandarizar la prueba del vórtice.

**Material y método:** Se evalúan la frecuencia de síntomas previos ante estímulos vibratorios mediante un cuestionario; la respuesta (aumento de perímetro del antebrazo, eritema, edema, calor; y, prurito) a la prueba de provocación del vórtice en una población de voluntarios sanos en 12 centros por dos evaluadores independientes en cada centro; la fiabilidad inter-evaluador; y, la correlación entre síntomas previos y reacción a la prueba de provocación.

Resultados: Participaron 140 voluntarios. 17 se excluyeron por dermografismo. La prueba del vórtice desencadenó eritema, calor o urticaria/edema localizado en el 58,5%; 38,2%; y el 32,5%, de los casos respectivamente. La concordancia entre evaluadores fue baja respecto del aumento del perímetro del antebrazo a tres alturas (coeficiente de correlación intraclase: 0,477 IC 95%: 0,253–0,634; 0,496 IC 95%: 0,280–0,647; y 0,370 IC 95%: 0,100–0,559, respectivamente) y óptima respecto del eritema, el calor y el edema localizado (índice Kappa: 0,868; .756; y .757, respectivamente). Se identificó una correlación significativa entre la puntuación del cuestionario y la respuesta al test en sus distintas variables (eritema, calor o edema localizado).

Conclusiones: Proponemos que el eritema; urticaria/edema localizado; y el calor; sustituyan a la variable de aumento de perímetro del antebrazo, como requisitos de respuesta positiva a la prueba del vórtice dadas su mayor facilidad de ejecución y el óptimo acuerdo entre evaluadores.

Palabras clave: Angioedema vibratorio; urticaria vibratoria; urticaria crónica inducible; urticaria crónica; vortex; ADGRE2.

“Erythema, localized edema and heat versus forearm perimeter increase. Time to revise the consensus recommendations for the vortex provocation test in vibratory urticaria-angioedema?”

## Abstract

Background and objective: Vibratory urticaria/angioedema is confirmed by the vortex provocation test. It has been agreed to measure the perimeter of the forearm after exposure to the vortex to define a positive response to it.

Material and method: We evaluated the frequency of prior symptoms following vibratory stimuli in volunteers (using a questionnaire); the response to the vortex test in the same volunteers (increase in forearm perimeter, erythema, localized edema, heat,

and pruritus); inter-rater reliability; and, the correlation between the questionnaire score and the response to the test.

Results: 140 volunteers participated. 17 were excluded due to dermographism. Of 123 without dermographism, 59% responded affirmatively to  $\geq 1$  item of the questionnaire. Localized erythema, heat or localized edema were observed in 58.5%; 38.2%; and 32.5%, respectively.

73,6% presented with itch. Mean intensity of itch was 3.44 95% CI (2.94-3.94).

Interrater agreement was low regarding the increase in forearm circumference at three levels (intraclass correlation coefficient: 0.477 95% CI: 0.253–0.634; 0.496 95% CI: 0.280–0.647; and 0.370 95% CI: 0.100–0.559, respectively); and, optimal regarding erythema, heat and localized edema (Kappa index: 0.868; .756; and .757, respectively). A significant correlation was identified between the questionnaire score and the altered response to the test in its different variables.

Conclusions: We propose the variables: erythema; localized edema; heat; and, the intensity/speed of onset/duration of pruritus, to define a positive response to the vortex test given their ease of execution and the optimal inter-observer agreement.

Key words: vibratory angioedema; vibratory urticaria; chronic inducible urticaria; chronic urticaria; vortex; ADGRE2.

#### Background and objective

Vibratory urticaria and angioedema are a group of conditions characterized by transient localized edema following a vibratory stimulus. A significant increase in histamine and other markers of mast cell degranulation in serum has been identified during episodes.

They can be categorized<sup>1</sup> as acquired (more common) or hereditary (exceptional).

Hereditary vibratory angioedema was originally described in 1972 by Patterson et al.<sup>2</sup> in a family whose members developed angioedema in response to vibratory stimuli shortly after birth. Forty-four years later, Boyden et al.<sup>3</sup> described 3 Lebanese families in which the Adhesion G Protein-Coupled Receptor E2 (ADGRE2) mutation was identified. Although both are hereditary, the cases reported by Patterson et al.<sup>2</sup> affected patients who developed angioedema lesions with a history of a few hours to a few days, whereas Boyden's cases<sup>3</sup> exhibited < 1-hour history transient urticaria lesions (wheals). Therefore, although the ADGRE2 mutation has not been studied in the patients of Patterson et al., it has been suggested that these represent 2 different entities, leading to the proposal of subcategorizing hereditary variants<sup>1</sup> into 2 subtypes: "Patterson-type hereditary vibratory angioedema<sup>2</sup>" and "Boyden-type hereditary vibratory urticaria<sup>3</sup>" both ADGRE2-related.

Acquired cases can also be subcategorized<sup>1</sup> into 2 categories: the more common type of "acquired vibratory angioedema"<sup>1</sup>, which affects patients with a month-or-year history of sporadic angioedema triggered by vibratory stimuli<sup>4–16</sup>, and the exceptional form of "secondary acquired vibratory urticaria"<sup>1</sup>, a transient condition presenting as wheals triggered by a vibratory stimulus in the context of a primary trigger (e.g., *Candida* infection<sup>17</sup> or hymenoptera sting<sup>18</sup>).

Most cases are triggered by the vibration inherent in certain occupational or recreational activities<sup>4</sup>, which can lead to significant work performance impairment<sup>16</sup>. When avoiding vibratory stimuli is not feasible—as in working environments—a good response to treatment with oral antihistamines or omalizumab has been described<sup>16</sup>.

Clinical history and response to the vortex test are essential for diagnosis confirmation purposes. According to the guidelines agreed upon by EAACI/GA2LEN/EDF/UNEV on the management of inducible urticaria<sup>19</sup>, it is recommended to expose the volar surface of the forearm to the vibration induced by a laboratory vortex mixer for 5 minutes (780–1,380<sup>0</sup> rpm) and then assess the test results 10 minutes later. The vortex test is considered positive if edema of the exposed area is observed (quantified as an increase in forearm circumference). Vibratory urticaria and angioedema can be misdiagnosed as other forms of inducible urticaria—dermographism or delayed pressure urticaria—if a thorough history and specific provocation tests are not performed<sup>16</sup>.



According to a recent review<sup>4</sup> on acquired vibratory angioedema, there is notable heterogeneity in the literature regarding running and interpreting the vortex provocation test. This test was performed in 8 out of 12 reports on acquired vibratory angioedema, and forearm circumference before and after the test was reported in only 2 of them. These findings highlight the need to standardize the protocol for the vortex provocation test.

Moreover, it has been found that a past personal history of symptoms in response to vibratory stimuli is significantly associated with altered responses to the vortex provocation test in a high proportion of individuals in healthy volunteer populations (41.3%-43%)<sup>20,21</sup> according to questionnaire-based studies.

### Material and methods

We designed a study (Fig. 1) to evaluate: descriptive statistics on the prior personal history of symptoms in response to vibratory stimuli in a population of volunteers; descriptive statistics of altered responses to the vortex provocation test (with respect to the following variables: erythema, urticaria or localized edema, warmth, forearm circumference increase, and the onset, intensity, speed of onset, and duration of pruritus); inter-rater reliability of the response to the test (comparing observations made by 2 independent researchers at each center); and the correlation between prior symptoms due to vibratory stimuli and the response variables of the vortex test (erythema, urticaria or localized edema, warmth, forearm circumference increase, and pruritus onset, intensity, speed of onset, and duration).

### Study population, involved centers, inclusion period, and inclusion/exclusion criteria

The study population included volunteers who were health care professionals who worked in 12 Dermatology Departments in Spain (Hospital Universitario de Toledo; Hospital Universitario Infanta Leonor; Hospital Universitario Infanta Sofía; Hospital Universitario de Móstoles; Hospital Rey Juan Carlos; Hospital Universitario de Fuenlabrada; Hospital Universitario Doce de Octubre; Hospital Universitario La Paz; Hospital Universitario Fundación Alcorcón; Hospital Universitario Puerta de Hierro-Majadahonda; Hospital Universitario Gregorio Marañón; and Hospital Universitario de Guadalajara) between January and July 2021. A minimum of 10 participants were included per hospital, including physicians, nurses, nursing assistants, and administrative staff.

*Inclusion criteria:* Adults capable of understanding and signing informed consent.

*Exclusion criteria:* Dermographism defined as the presence of a wheal or linear hive appearing 10 minutes after applying friction with a blunt object (FricTest<sup>®</sup>, pen, or dermatographometer).

#### Tools used

1. A questionnaire (Table 1) was administered to evaluate the past personal history of symptoms—frequency of pruritus or edema—in response to vibratory stimuli, with scores ranging from 0 to 30 in each case.
2. A laboratory vortex mixer at 1,200 rpm was used as the provocation test tool. The volar surface of each participant's forearm was exposed to vibration induced by this device for 5 minutes. The same vortex model was used across all participant centers (Four E's Scientific Digital Vortex Mixer, model: MI0101002D, movement type: orbital; orbital diameter: 6 mm; speed range: 0-3,000 rpm) (Fig. 2).

Prior to the test, at each center, 2 independent researchers measured the forearm circumference at 3 levels: proximal (below the antecubital flexure), distal (at wrist level of the styloid process), and a midpoint between the 2. Multiple reference points were marked with surgical markers for consistency.

Ten minutes after completing the vibratory stimulus, the researchers conducted new measurements at the same levels. Additionally, they recorded the presence/absence of erythema, warmth, urticaria, or localized edema vs the contralateral forearm which remained non-exposed to the stimulus. Localized edema was defined as areas of linear edema corresponding to the regions in contact with the edges of the vortex plate—the point of highest vibration intensity—including < 1-hour history superficial linear wheals and deeper, longer-lasting angioedema lesions.

3. A visual analog scale was used by participants to evaluate the intensity, speed of onset, and duration of pruritus (the only subjective response variable).
4. For the dermatographism provocation test, FricTest<sup>®</sup>—a dermatographometer—or a blunt object was used, depending on availability at each center, immediately after the cessation of vibration. The presence/absence of dermatographism was read and recorded 1<sup>o</sup> minutes after stopping vibration, immediately before recording the other variables.

## Statistical analysis

The reproducibility of the diagnostic tests was analyzed using the intraclass correlation coefficient (ICC) and the kappa index for quantitative and qualitative variables, respectively. To evaluate the correlation between the final score of the previous symptom questionnaire and the vortex test response variables, we used Pearson/Spearman correlation coefficients for quantitative variables.

Data recording, both by the investigators at each center (regarding objective variables such as the presence of erythema, heat, hives, or localized edema, or the measurements of the forearm perimeters), and the participants (subjective variables related to itching, and responses to the previous symptom questionnaire with vibratory stimuli), was conducted using a double-blind procedure to make sure that the interpretation of the vortex test response by the investigators was not affected. The study methodology is shown in Figure 1.

## Results

A total of 140 volunteers were evaluated, 17 of whom exhibited dermographism and were excluded. A total of 59% of the 123 participants without dermographism responded affirmatively to, at least, 1 item on the symptoms questionnaire. The mean questionnaire score was 2.02, 95%CI, 1.53–2.50.

An altered response to the vortex test was observed for the qualitative variables: erythema, warmth, or urticaria/localized edema in 58.5%, 38.2%, and 32.5% of cases, respectively (Fig. 3).

Pruritus onset was reported by 73.6% of participants. The mean pruritus intensity (as estimated by participants using a visual analog scale from 1 to 10) was 3.44, 95%CI, 2.94–3.94.

The ICC used to evaluate inter-rater concordance for forearm circumference increases measured at 3 different levels was: 0.477, 95%CI, 0.253–0.634; 0.496, 95%CI, 0.280–0.647; and 0.370, 95%CI, 0.100–0.559, respectively. The kappa index used to evaluate inter-rater reliability for qualitative dichotomous variables, such as erythema, warmth, and urticaria or localized edema, was 0.868, 0.756, and 0.757, respectively.

The bivariate analysis (Mann-Whitney test) revealed a significant correlation between the total questionnaire score and the qualitative variables erythema, warmth, and urticaria/localized edema: Asymptotic Significance (Asymp Sig) for two-tailed tests: 0.000, 0.013, and 0.001, respectively.

A multivariate logistic regression analysis was performed, but combining variables did not achieve greater significance.

According to the Mann-Whitney U test for independent samples, no significant correlation was reported between the presence of pruritus and the questionnaire score (0.285). However, a significant Spearman's rank correlation coefficient was found between the questionnaire score and the intensity, onset time, and duration of pruritus: two-tailed Asymp Sig: 0.002, 0.025, and 0.001, respectively.

## Discussion

Symptoms triggered by vibratory stimuli and altered responses to the vortex provocation test turned out to be a common finding in our population of health care professional volunteers across 12 dermatology departments in Spain. The percentage of affected volunteers (59%) was even higher than previously reported figures in similar studies published in the literature (41.3–43%)<sup>20, 21</sup>.

The high frequency of symptoms (pruritus, erythema, or edema) triggered by vibratory stimuli in this and other groups of otherwise healthy volunteers<sup>20, 21</sup> raises the practical difficulty of establishing a threshold to differentiate between physiological and pathological responses, similar to how thresholds are applied in other inducible urticarias (e.g., simple and symptomatic dermatographism)<sup>4</sup>. It is possible that the classification of these responses as pathological likely depends on the degree of functional impairment and the quality-of-life deterioration due to mandatory exposure to vibratory stimuli, especially in occupational contexts<sup>4</sup>.

In our study, significant agreement between evaluators was observed regarding qualitative objective response variables in the vortex test (erythema, urticaria/localized edema, and warmth), as expected, since these variables are easy to assess by comparing the exposed and non-exposed forearm skin.

Additionally, we identified a significant correlation between these variables and the total questionnaire score, suggesting that individuals who recall prior symptoms in response to vibratory stimuli are more likely to develop an abnormal test response in terms of erythema, warmth, urticaria, or localized edema.

We also observed a significant correlation between the questionnaire score and the intensity, onset speed, and duration of pruritus, but not with the presence/absence of pruritus. This suggests that vibration may physiologically induce a mild degree of transient pruritus in some individuals with a normal test response, unlike individuals with altered responses (in terms of erythema, warmth, or urticaria/localized edema), who tend to experience earlier, more intense, and longer-lasting pruritus.

Our study found poor inter-rater reliability regarding the increase in forearm circumference, with a low intraclass correlation coefficient. We believe this may be related to the challenges investigators faced in taking forearm circumference measurements at precisely the same level before and after the test, despite meticulous use of surgical marker reference points on both sides of the forearm and efforts to apply uniform pressure with the measuring tape.

The increase in forearm circumference was described in the EAACI/GA2LEN/EDF/UNEV 2016 consensus on the management of inducible chronic urticaria as an objective parameter to quantify the vortex test response. In our opinion, the value of this consensus recommendation should be revisited due to the lack of inter-rater reliability and practical difficulties reported. These findings add to the scarce literature references on how the test should be run <sup>4</sup>, where most studies do not report or mention the measurement of forearm circumference. When reported, differences in circumference before and after the test are minimal, often falling within the margin of measurement error, rendering them non-significant.

In contrast, the assessment of erythema, warmth, or urticaria/localized edema is straightforward compared with the contralateral forearm. These variables also demonstrate optimal inter-rater reliability and correlate significantly with the questionnaire on prior symptoms following vibratory stimuli.

We acknowledge that our results apply to unselected volunteer individuals. Further studies are needed to evaluate the behavior of all response variables to the vortex provocation test in patients suspected of having vibratory urticaria or angioedema.

## Conclusions

In conclusion, we highlight the high frequency of prior symptoms in response to vibratory stimuli among a group of healthy volunteers. Additionally, we emphasize the significant correlation between this history (total questionnaire score) and altered responses to the test across different variables.

Based on the results of this study, we suggest that the proposal outlined in the 2016 EAACI/GA2LEN/EDF/UNEV consensus document regarding forearm circumference measurement as a marker of positivity to the vortex provocation test in vibratory urticaria or angioedema is inadequate due to high inter-individual variability in observations.

We propose that other response variables, not previously considered in the consensus document—such as erythema, urticaria, localized edema, or warmth—should replace forearm circumference measurement and be considered requirements to define a positive response to the vortex provocation test. These variables are easier to assess, demonstrate optimal inter-rater reliability, and correlate with the total questionnaire score on prior symptoms. In other words, we propose that the provocation test should be considered positive if vortex-induced vibration triggers erythema, urticaria, localized edema, or warmth.

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## Ethical responsibilities

The study was approved by the Clinical Research Ethics Committee for Medicinal Products (Complejo Hospitalario Universitario de Toledo, registration No. 721) and then by the ethics committees of the other participant centers. Participation was voluntary, and all participants signed an informed consent document.

## Conflicts of interest

None declared.

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Figure 1. Diagram of the study design.

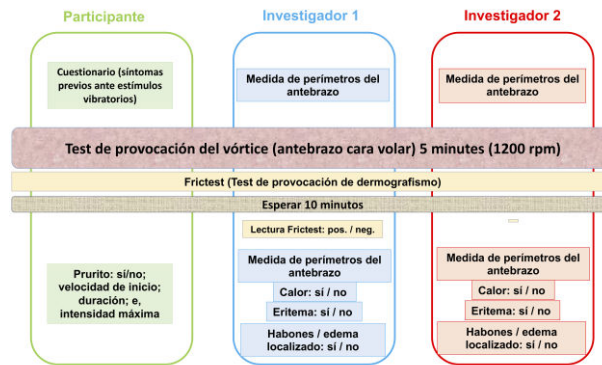


Figure 2. Photograph showing the position of the forearm on top of the laboratory vortex mixer during the provocation test (vortex test).



Figure 3. A) Erythema on the stimulated forearm of a participant. B) Linear edema and erythema affecting the skin of the forearm exposed to maximum vibratory stimulus in the area in contact with the edge of the vortex plate. C) Linear edema and urticaria affecting another participant.

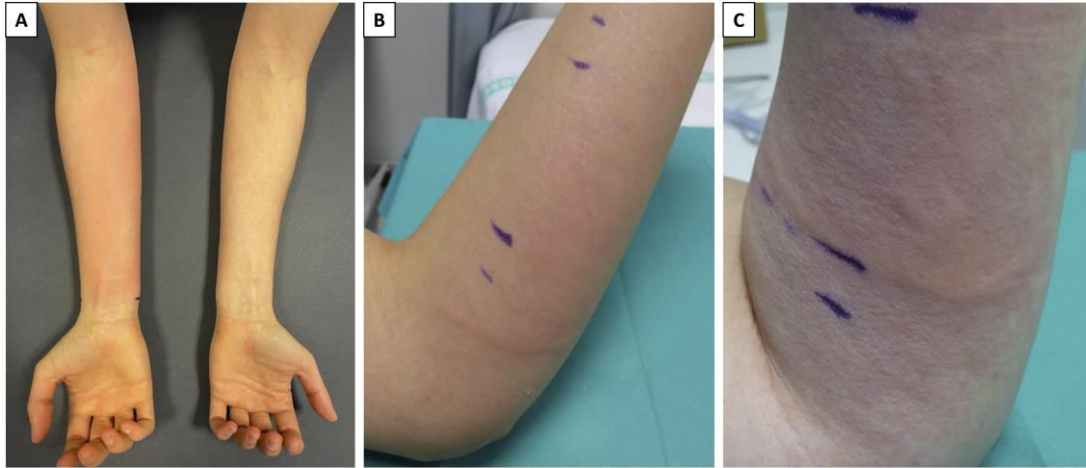


Table 1. Questionnaire on previous reactions to vibratory stimuli

Have you ever experienced symptoms such as itching, swelling, or welts when exposed to any of the following stimuli?	Never (0)	Occasionally (1)	Often (2)	Always or almost always (3)
1. Walking, running, or exercising on uneven terrain				
2. Clapping				
3. Hot tubs, bathtubs, or hydro-massage showers				
4. Vigorous massages (manual, air chambers, or massage devices)				
5. Shaking objects (rattles, shakers, etc.)				
6. Pushing a shopping cart, baby stroller, suitcase, or similar items on uneven terrain				
7. Riding a bicycle or motorcycle on uneven terrain				
8. Machinery (drills, electric saws, woodworking grinders, jackhammers, lawnmowers, spray guns, lathes, sewing machines, etc.)				
9. Driving a car or another type of vehicle (steering wheel vibration)				
10. Other vibrating objects (electric toothbrushes, keyboards, sex toys, dental procedures, vibrating platforms at gyms, blenders, etc.)				

## TRADUCCIÓN DE LA FIGURA 1 (NEGRO: ESPAÑOL · AZUL: INGLÉS)

Participante

Cuestionario (síntomas previos ante estímulos vibratorios)

Prurito: sí/no; velocidad de inicio; duración; e intensidad máxima

Investigador 1

Medida de perímetros del antebrazo

Calor: sí/no

Eritema: sí/no

Habones/Edema localizado: sí/no

Investigador 2

Medida de perímetros del antebrazo

Calor: sí/no

Eritema: sí/no

Habones/Edema localizado: sí/no

Test de provocación del vórtice (antebrazo cara volar) 5 minutos (1200 rpm)

Frictest (Test de provocación de dermatografismo)

Esperar 10 minutos

Lectura Frictest: pos./neg.

Participant

Questionnaire (prior symptoms in response to vibratory stimuli)

Itching: yes/no; onset speed; duration; and maximum intensity

Investigator 1

Measurement of forearm circumference

Heat: yes/no

Redness: yes/no

Wheals/Localized edema: yes/no

Investigator 2

Measurement of forearm circumference

Heat: yes/no

Redness: yes/no

Wheals/Localized edema: yes/no

Vortex provocation test (volar side of forearm) for 5 minutes (1200 rpm)

FricTest (Dermographism provocation test)

Wait 10 minutes

FricTest reading: pos./neg.