



## Review

# Electrographic indices in migraine patients: A systematic review and meta-analysis



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## ABSTRACT

**Background and aim:** Migraine patients can exhibit autonomic dysregulation, in turn leading to cardiac conduction and repolarization abnormalities. This systematic review and meta-analysis evaluated the electrocardiographic changes in migraineurs.

**Method:** PubMed and Embase databases were searched for human studies using the search terms 'migraine' and 'electrocardiogram' until 15th December 2018, identifying 108 and 131 studies.

**Results:** Thirteen studies involving 667 migraineurs and 208 normal subjects included (mean age = 30.7, total male percentage = 19.8%) were included. A longer mean QTc interval (standard mean difference = 7.89, 95% confidence interval = [3.29, 12.49],  $p = 0.0008$ ) and higher frequency of QTc prolongation (risk ratio [RR] = 6.23, [2.86–13.58],  $p < 0.00001$ ), but no difference in PR-interval (SMD = 4.33, [−3.90–12.56],  $p = 0.30$ ) were observed during migraine attacks compared to pain-free periods. P-wave dispersion was higher in migraine patients compared to controls (mean difference = 3.62, [1.03–6.21],  $p = 0.006$ ). RR-interval were statistically indistinguishable between migraine patients and controls (SMD = 0.08, [−0.65–0.81],  $p = 0.83$ ), or between migraineurs with and without aura (SMD = −0.03, [−0.44–0.38],  $p = 0.89$ ). Deep breathing ratio was significantly lower in migraineurs compared to controls (SMD = −0.27, 95% CI = [−0.46, −0.08],  $p = 0.006$ ) but similar between migraineurs with and without aura (SMD = −0.04, [−0.27–0.19],  $p = 0.74$ ). No significant difference in Valsalva ratio is found between migraineurs and controls (SMD = 0.10, [−0.32–0.53],  $p = 0.63$ ) or between migraineurs with and without aura (SMD = −0.17, [−0.40–0.06],  $p = 0.14$ ). Root mean square of successive differences (RMSSD) (SMD = −0.07, [−1.10–0.95],  $p = 0.89$ ) and standard deviation of NN intervals (SDNN) (SMD = −0.10, [−0.61–0.41],  $p = 0.71$ ) did not significantly differ between migraine patients and controls.

**Conclusion:** Electrocardiographic alterations are observed in migraine patients compared to controls, especially during migraine attacks.

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## Introduction

Migraine is a highly disabling brain disorder with symptoms such as throbbing headache, light and sound sensitivity that affects approximately 15% of the global adult population [1,2]. It has long been known that migraine involves autonomic dysfunction, but the precise pathophysiology remains unclear and evidence is often contradictory. Migraine patients can be subdivided based on the presence or absence

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of aura. Aura is a neural-driven visual, auditory or motor disturbance, and it is found to manifest in around 30% migraine patients [1,3]. Although the occurrence of aura is long theorized to be triggered by cortical spreading depression (CSD), the relationship between CSD and the occurrence of migraine with its associated autonomic dysregulation remain to be unclear [4,5]. Cardiac electrical conduction, which is under rigorous autonomic control, can reflect the autonomic disturbances in migraine patients. Therefore, by comparing observing the difference in changes of the electrocardiogram (ECG) between migraineurs and control, migraineurs with and without aura, non-ictal and ictal periods, insights towards details in autonomic imbalance can be obtained.

In the past, autonomic imbalance in migraine is mainly examined through heart rate variability (HRV) studies. Since HRV is based on oscillations in RR-interval under different contexts, it does not reflect specific alterations in cardiac conduction [6]. Recently, more studies are conducted on changes in electrocardiographic parameters in addition to RR-interval. However, there is yet to be a meta-analysis that pools data on the various electrocardiographic changes associated with migraine. By analyzing studies on electrocardiographic changes presented in migraineurs, the present meta-analysis aims to generate a more holistic understanding of the autonomic dysregulation in migraine, and the resulting cardiac conduction abnormalities. It includes observational studies comparing ECG changes between migraine patients and normal individuals, patients with and without aura, during migraine attack and pain-free period.

## Method

### Search strategy

This study is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. Two databases, PubMed and Embase, were searched for human studies using both the search terms “electrocardiogram” and “migraine”, including synonyms and relevant abbreviations. The databases were searched up to December 15th, 2018, with no language restrictions. The title and abstract of the identified studies are then screened for eligibility. Full text of the eligible studies is then retrieved for the assessment of compliance against the inclusion criterion. Studies were excluded at the initial screening, or the later assessment if any of the exclusion criteria is met.

### Inclusion and exclusion criteria

The following inclusion criterion is applied to identify eligible studies: 1) the study is an observational study on human subjects with migraine diagnosed under criterion by the International Headache Society; 2) comparison of ECG changes between migraineurs and healthy individuals, migraineurs with and without migraine, or during migraine attack and pain-free period is performed; 3) subjects examined are not under any specific migraine treatments, or taking medications that causes changes in cardiac rhythm.

At the initial screening, studies are excluded if they: 1) are duplicated under the search of two databases; 2) are case reports, reviews or meta-analyses; 3) are irrelevant. Eligible studies are excluded at further assessment if they: 1) are not an observational study; 2) contain insufficient data for further statistical analysis; 3) lack comparison between subject groups; 4) measured ECG parameters that are not used in at least one other study.

### Data extraction and statistical analysis

Studies compliant with the inclusion criterion were selected for the meta-analysis, and data extracted were then entered into a standardized Microsoft Excel spreadsheet. The following data were extracted: 1) publication details (surname of first author and publication year);

2) details of subjects studied (age, sex, presentation of aura); 3) ECG parameters measured. Measurements of ECG parameters for subgroups, e.g. migraineurs with aura and migraineurs without aura, are pooled to generate the measurement for the combined group, e.g. migraineurs.

Statistical analysis of the pooled data is delivered using the Reviewer 5.3 software. For the selection of effect model used on the pooled data, the  $I^2$  statistic, which represents inter-study variance from heterogeneity, is used [8]. An  $I^2$  value of <50% indicates low heterogeneity, hence the fixed-effects model was used [9]. When  $I^2$  value was >50%, the random-effects model was adopted to account for the other random variables that contribute to the difference in results between the studies. For continuous variables, the standard mean difference between subject groups was calculated. The risk ratio between subject groups for the occurrence of ECG abnormalities is also calculated. 95% confidence interval is supplemented for both the standard mean difference and risk ratio found. Statistical significance was defined as a two-tailed  $p$ -value of 0.05.

### Quality analysis

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the included studies [10]. The NOS point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: a) representativeness of the exposed cohort; b) selection of the non-exposed cohort; c) ascertainment of exposure; d) demonstration that outcome of interest was not present at the start of study; e) comparability of cohorts based on study design or analysis; f) assessment of outcomes; g) follow-up periods that were sufficiently long for outcomes to occur; and h) adequacy of follow-up of cohorts. This scale ranged from zero to nine stars, which indicated that studies were graded as poor quality if the score was <5, fair if the score was 5 to 7, and good if the score was >8.

## Results

### Search result and study characteristics

A flow diagram of the search process for the selection of studies, including the search terms, inclusion and exclusion criterion is shown in Fig. 1. In total, 108 and 131 studies were identified in PubMed and Embase respectively. After the initial screening and further assessment, 13 studies met all inclusion criterion and were included in the meta-analysis. One study is added to the meta-analysis under reviewer suggestion. Amongst the 14 studies, four studies compared both the average QTc interval and the number of QTc prolongation during migraine attack and pain-free period [11–14]. RR-interval is compared between migraineurs and control by four studies [15–18], and three studies compared between migraineurs with and without aura [13–15]. Two studies compared the PR-interval duration during the attack and pain-free period [12,13], and three studies compared the P-wave dispersion (PWD) between migraineurs and control [19–21]. A total of six studies compared the HRV between migraineurs with and without aura, and migraineurs and controls. HRV was derived from the variations in RR-interval under different circumstances. Within these six studies, three compared the deep breathing ratio between migraineurs with and without aura, and migraineurs and controls [17,22,23]. Similarly, four studies compared the Valsalva ratio between controls and migraineurs, and migraineurs with and without aura [16,17,22,23]. The remaining two studies compared the root mean square of the successive differences in RR intervals (RMSSD) and standard deviation of NN (RR) intervals (SDNN) between migraineurs and control [15,24]. In total, 667 migraineurs and 208 normal subjects were included (mean age = 30.7, total male percentage = 19.8%). In the cohort of migraine patients, 31.1% suffer from migraine with aura.

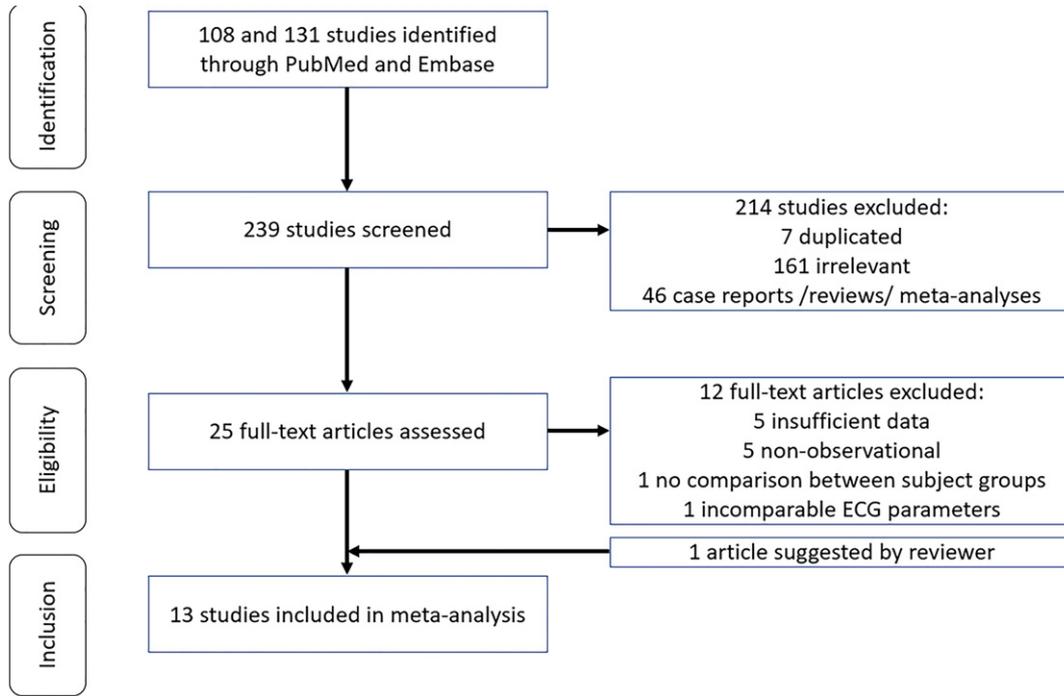


Fig. 1. PRISMA diagram of the search and study selection process.

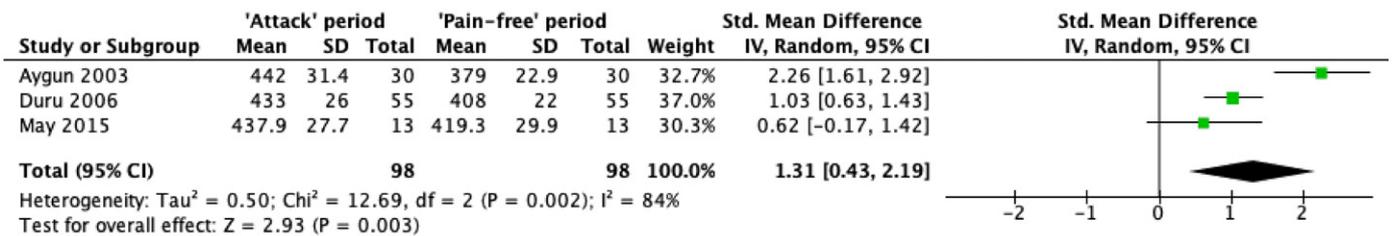
The characteristics of the selected studies are presented in Supplementary Table 1, including first author, publication year, number of subjects in different subgroups, age, the proportion of male, the proportion of migraineurs with aura, and data groups compared in the study. Quality analysis by the NOS is shown in Supplementary Table 2.

*Electrographic changes*

The electrographic parameters analyzed are QTc interval, number of QTc prolongations, PWD, RR-interval and PR-interval. Migraineurs are found to experience longer QTc intervals (SMD = 7.89, 95% CI =

[3.29, 12.49],  $p = 0.0008$ , Fig. 2A), and significantly more QTc prolongations during migraine attacks than pain-free periods (RR = 6.23, 95% CI = [2.86, 13.58],  $p < 0.00001$ , Fig. 2B) [4–6,14]. Given the positive range of the 95% CI and the extremely low  $p$ -value for both figures, strong evidence supports the significant association between migraine attacks and increased QTc prolongation. Large heterogeneity is observed in the measurement of QTc interval ( $I^2 = 99\%$ ,  $p \leq 0.00001$ ), while homogeneity is observed in recording of QTc prolongation number ( $I^2 = 0\%$ ,  $p = 0.48$ ). Moreover, a significant increase in PWD is also found in migraine patients comparing to controls (mean difference = 3.62, 95% CI = [1.03, 6.21],  $p = 0.006$ , Fig. 3) [19–21]. Similar to the comparison of

A. QTc interval during attacks vs. pain-free periods



B. Number of QTc Prolongation during attacks vs. pain-free periods

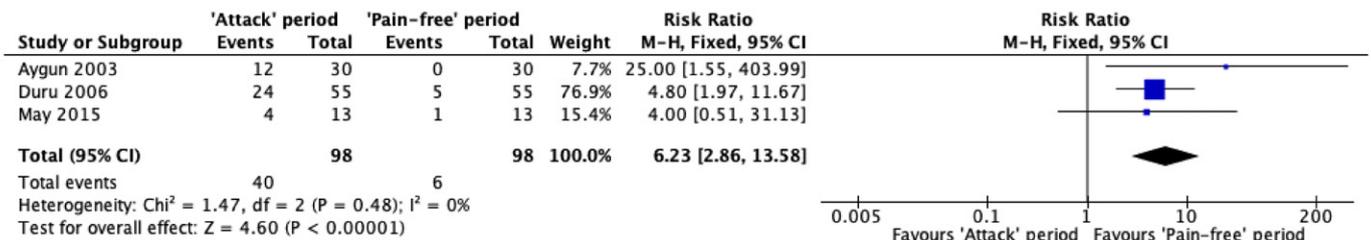


Fig. 2. A. QTc interval during attacks vs pain-free periods. B. Number of QTc Prolongation during attacks vs pain-free periods.

## PWD in migraine patients vs. controls

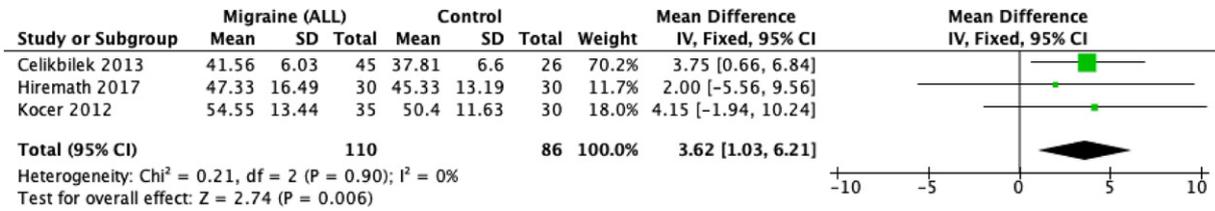


Fig. 3. P-wave dispersion (PWD) in migraine patients vs. controls.

QTc interval, the positive range of CI and  $p$ -value  $< 0.05$  supports a significant relationship between migraine and increase in PWD. No heterogeneity is observed ( $I^2 = 0\%$ ,  $p = 0.90$ ). In terms of PR-interval, there is no significant difference in its duration during migraine attack and pain-free period (SMD = 4.33, 95% CI = [-3.90, 12.56],  $p = 0.30$ ) [5,6]. Although the  $p$ -value is  $> 0.05$ , with only two studies analyzed, a conclusive remark cannot be made towards the relationship between the length of the PR interval and migraine attacks. The significant heterogeneity ( $I^2 = 99\%$ ,  $p < 0.0001$ ) highlights the substantial inter-study variation, suggesting the need for more studies to be conducted in this area for analysis to be effective. In terms of RR-interval, no significant difference is found comparing between migraineurs and controls (SMD = 0.08, 95% CI = [-0.65, 0.81],  $p = 0.83$ , Fig. 4A) [15–18], or between migraineurs with and without aura (SMD = -0.03, 95% CI = [-0.44, 0.38],  $p = 0.89$ , Fig. 4B) [13–15]. Substantial heterogeneity is observed in the comparison between migraineurs and controls ( $I^2 = 84\%$ ,  $p = 0.0004$ ), while homogeneity is reported in the comparison between migraineurs with and without aura ( $I^2 = 0\%$ ,  $p = 0.89$ ).

## Heart rate variability

Heart rate variability is derived from changes in RR-interval from its baseline value under different contexts. Compare to healthy subjects, a significant reduction in deep breathing ratio is observed in migraine patients (SMD = -0.27, 95% CI = [-0.46, -0.08],  $p = 0.006$ , Fig. 5A) [7–9]. However, deep breathing ratio did not differ significantly between migraineurs with and without aura (SMD = -0.04, 95% CI = [-0.27, 0.19],  $p = 0.74$ , Fig. 5B) [7–9]. Homogeneity is observed in both comparisons between migraineurs and controls ( $I^2 = 0\%$ ,  $p = 0.57$ ), and between patients with and without aura ( $I^2 = 0\%$ ,  $p = 0.87$ ). Furthermore, no significant difference is observed in Valsalva ratio between migraineurs and controls (SMD = 0.10, 95% CI =

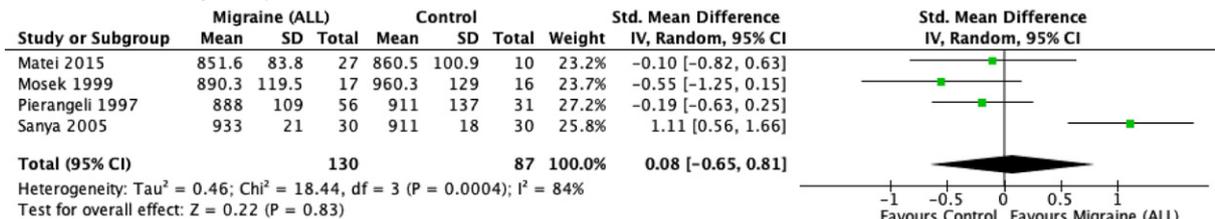
[-0.32, 0.53],  $p = 0.63$ , Fig. 6A), and migraineurs with and without aura (SMD = -0.17, 95% CI = [-0.40, 0.06],  $p = 0.14$ , Fig. 6B), with large and little heterogeneity respectively ( $I^2 = 77\%$ ,  $p = 0.63$ ;  $I^2 = 29\%$ ,  $p = 0.14$ ) [14,15,20,21]. Additionally, no significant difference in RMSSD was found between migraine patients and normal controls (SMD = -0.07, 95% CI = [-1.10, 0.95],  $p = 0.89$ ) with marked heterogeneity ( $I^2 = 74\%$ ,  $p = 0.05$ ) [11,12]. Similarly, SDNN between migraineurs and controls are not found to differ significantly (SMD = -0.10, 95% CI = [-0.61, 0.41],  $p = 0.71$ ) with no heterogeneity ( $I^2 = 0\%$ ,  $p = 0.71$ ).

## Discussion

There are several significant findings from the present meta-analysis: 1) migraineurs experience longer QTc interval, and are more likely to experience QTc prolongation during migraine attack than pain-free period; 2) migraineurs have greater PWD than controls; 3) deep breathing ratio is reduced in migraineurs compared to controls. Insignificant differences are found in 1) PR-interval between attack and pain-free period; 2) RR-interval, Valsalva ratio, RMSSD and SDNN between migraineurs and controls; 3) RR-interval, deep breathing ratio and Valsalva ratio between migraineurs with and without aura.

It is known that autonomic balance is key to the control of QTc interval [25]. Although sympathetic activation stimulates both depolarizing and repolarizing currents, increased QTc prolongation under increased sympathetic activation has been observed by other studies, which is attributed to the predominant effect of beta-mediated increase in L-type  $\text{Ca}^{2+}$  current [26,27]. A potential explanation for the phenomenon is the hypersensitivity of adrenoceptors under the downregulation of norepinephrine release under repeated depletion from migraine attacks, which is supported by the lower baseline plasma norepinephrine level and the pressor hyperresponsiveness to phenylephrine found in

## A. RR-interval in migraine patients vs. controls



## B. RR-interval in migraine patients with auras vs. without auras

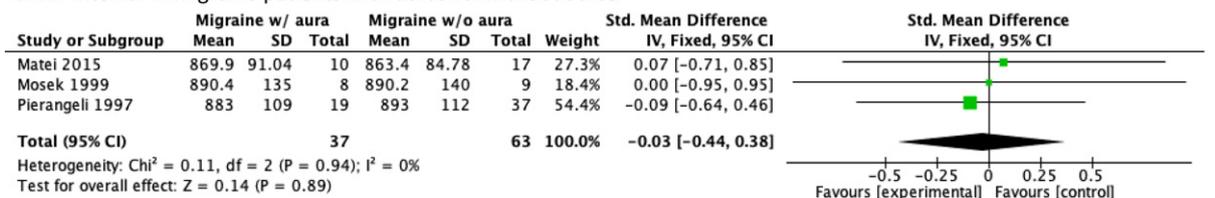
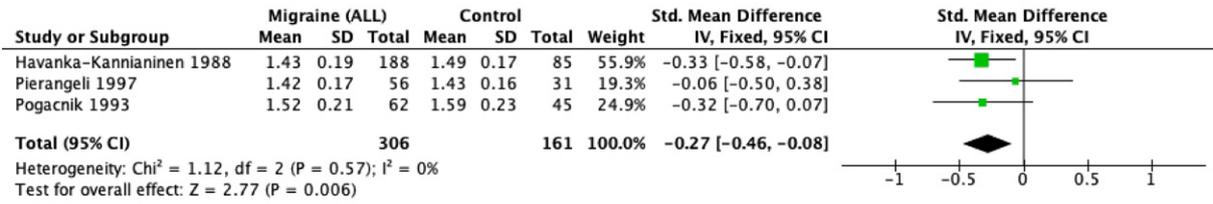


Fig. 4. A. RR-interval in migraine patients vs. controls. B. RR-interval in migraine patients with auras vs. without auras.

A. Deep breathing ratio in migraine patients vs. controls



B. Deep breathing ratio in migraine patients with auras vs without auras

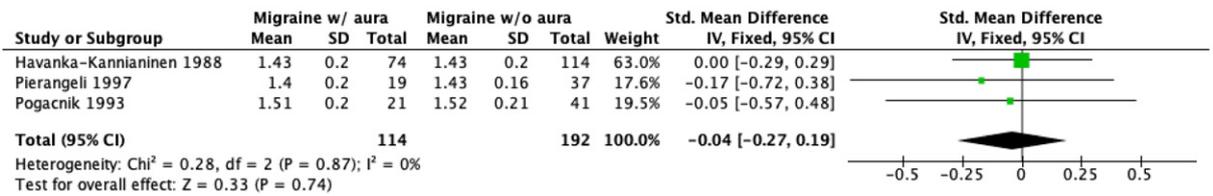


Fig. 5. A. Deep breathing ratio in migraine patients vs. controls. B. Deep breathing ratio in migraine patients with auras vs without auras.

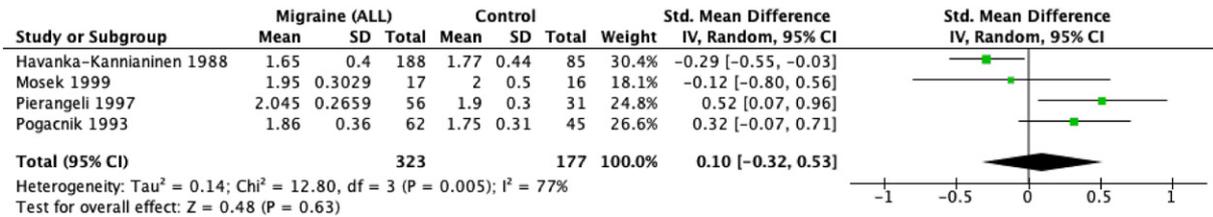
migraineurs [28,29]. Unfortunately, none of the included studies examined QRS duration between attack and pain-free period, hence the autonomic effects on ventricular depolarization and repolarization cannot be distinguished. Prolonged QRS duration in migraineurs is observed in one of the included studies, which may provide indirect evidence for low baseline norepinephrine level [21]. Other factors, such as migraine medications and vasospasm, can also be attributed to the increased incidence of QTc prolongation. It has been reported that the use of triptans can result in coronary vasospasm and hence QT prolongation [30,31]. Therefore, the concurrent use of migraine medications by migraineurs may have contributed to the increased incidence in QTc prolongation.

Although PWD generally decreases under increased sympathetic tone, the paradoxical increase may be attributed to the norepinephrine downregulation. The absence of significant difference in PR-interval between attack and pain-free period, despite the hypothesized sympathetic hyperfunction, can also be justified by the norepinephrine depletion and corresponding increase in sympathetic co-transmitters [32]. Besides from the direct influence of sympathetic hyperactivity, increased inhomogeneous activation, intra-atrial and inter-atrial

electromechanical delays under autonomic-related structural and electrophysiological changes may also contribute to the increased PWD [19]. It is interesting to note that in both Kocer and Hiremath's studies, although the mean PWD in migraineurs is greater than controls, the difference is not statistically significant [20,21]. The increase in statistical significance in the pooled data suggests that studies of larger sample size are needed for relationships between migraine and electrocardiographic changes to be clearly identified.

The lack of difference in Valsalva ratio, RMSSD, and SDNN between migraineurs and controls, suggest unchanged autonomic cardiovascular reflex in spite of the overall autonomic dysregulation in migraine. The Valsalva ratio is derived by the maximum heart rate by the minimum heart rate after the Valsalva maneuver, and reflects the parasympathetic and sympathetic interaction in baroreflex in response to blood pressure changes [33,34]. RMSSD and SDNN are indicators for primarily vagal-mediated changes in RR intervals [6]. A lack of significant differences in RMSSD and SDNN indicates little change to parasympathetic vagal control [6]. The deep breathing ratio, derived from the division of maximum and minimum RR-interval of the subject during a period of deep breathing, is an indicator of parasympathetic function [22]. The

A. Valsalva ratio in migraine patients vs. controls



B. Valsalva ratio in migraine patients with auras vs. without auras

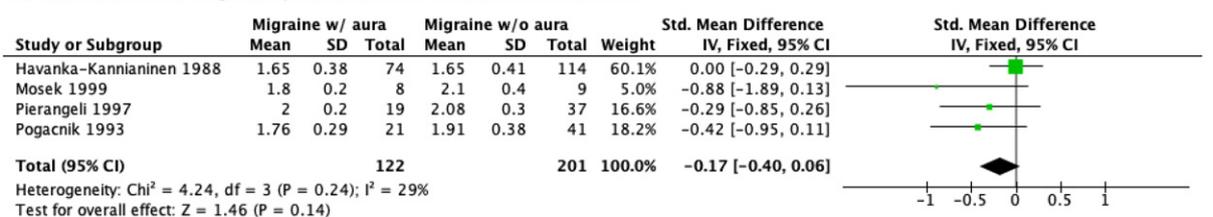


Fig. 6. A. Valsalva ratio in migraine patients vs. controls. B. Valsalva ratio in migraine patients with auras vs. without auras.

significant reduction in only the deep breathing ratio suggests that while parasympathetic hypofunction is present in migraineurs, the extent of impairment is mild [34]. Another study reported a significant reduction in Valsalva ratio only during attack, suggesting that the parasympathetic hypofunction is normally mild, and only worsens to the extent that impairs baroreflex during ictal periods [35]. Since the included studies measured the Valsalva ratio of migraineurs during headache-free periods, the mild parasympathetic hypofunction results in the lack of significant difference.

The little impact of aura upon the autonomic imbalance in migraine is presented through the limited difference in RR-interval and HRV parameters (deep breathing ratio, Valsalva ratio) in migraineurs with and without aura. This is supported by other studies that examined the autonomic dysregulation in migraine through other approaches [36]. It is possible that changes to autonomic balance by CSD are localized in the brain, therefore has limited impact upon cardiac conduction. Enhanced vascular reactivity with largely unchanged cardiac regulation in migraineurs after deep breathing test and Valsalva maneuver has been previously reported [37].

There are several limitations that should be noted for this meta-analysis. First of all, it should be acknowledged that data from a small number of studies, with relatively small sample sizes, are pooled for each ECG parameter. For PR-interval, RMSSD, and SDNN, only two studies are analyzed. Therefore, inconclusive remarks are made in the interpretation of PR-interval, and analysis of other parameters is used to support the interpretation of RMSSD and SDNN. Given the limited data available, subgroup analysis cannot be conducted. Furthermore, it has been reported that HRV studies tend to demonstrate greater parasympathetic impairment than autonomic cardiovascular reflex studies, which presents questions to the extent of parasympathetic hypofunction observed in migraine patients [38]. Moreover, the frequency-domain measurements for HRV studies are not included, therefore the sympathetic and parasympathetic contribution to HRV cannot be compared. Finally, the present meta-analysis only included studies that can be found on PubMed and Embase, hence studies absent on these two databases may be omitted.

## Conclusion

Electrocardiographic changes in migraine patients in comparison to normal subjects, and during migraine attacks demonstrate the dynamic autonomic impairment in migraine, where both sympathetic and parasympathetic systems are impaired to different extents, with differences between ictal and interictal periods. Significant sympathetic hypofunction and mild parasympathetic hypofunction in migraine are reflected by the ECG values. In addition, structural changes may be induced upon the heart under the autonomic disturbance, resulting in conduction abnormalities, hence explains the elevated risk of arrhythmia in migraineurs. Further research needs to be conducted on the difference of electrocardiographic changes between migraineurs with and without aura to examine the association between the presence of aura and difference in the autonomic impairment.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jelectrocard.2019.05.018>.

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