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Cardiovascular sympathetic nervous system response to cold pressor test among patients with migraine

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ABSTRACT

Context: Autonomic nervous system (ANS) dysfunction is one of the main characteristics of migraine; however, the exact relationship between migraine and ANS is not clear. Moreover, researches in this field yielded inconclusive and conflicting results. *Aims:* We tried to evaluate sympathetic autonomic cardiovascular response to cold stress in migraine patients and compare it to control group. *Methods and Material:* Cardiovascular responses to cold pressor test was evaluated in 91 participants, 61 participants were migraineurs (53 females and 8 males, average age 28.42±3.85 years) and 30 subjects were age and sex matched healthy controls (26 females and 4 males, average ages of 28.79±2.99 years). *Results:* Patient with migraine showed higher systolic and diastolic blood pressure in response to cold stress compared to controls ($P<0.05$), there were no differences between migraine patient with and without aura ($P>0.05$). Also, our data revealed a direct relationship between migraine duration and sympathetic response. *Conclusions:* Migraineurs have higher sympathetic tone compared to controls; Sympathetic hyperactivity is not significantly different between migraineurs with aura and without aura. A direct relationship between sympathetic over-activity and migraine duration was observed in patients group. *Key message:* Migraineurs have a higher sympathetic tone making patients more vulnerable to cerebrovascular disease (CVD). So, clinicians should take care that some medications used in migraine management may affect cardiovascular system, and should try to prevent the modifiable CVD risk factors among migraineurs.

Keywords: Headache, migraine, autonomic dysfunction, cerebrovascular disease, cold pressor test.

1. INTRODUCTION

Many studies confirm that migraine, especially migraine with aura (MA) increase risk of brain ischemic vascular events (Buring JE et al., 1995; Etminan M et al., 2005; Gryglas A and Smigiel R 2017; Sacco S and Kurth T 2014), even after adjusting cardiovascular risk factors especially in young female migraineur with aura (Carolei A, Marini C, and De MG 1996; Tzourio C et al., 1995). This was attributed to repeat exposure to cortical spreading depression (CSD), which activate a cascade of inflammatory events, and eventually to organic brain damage (Bigal ME et al., 2009). While the link between migraine and increased risk of hemorrhagic stroke is still controversial, some studies found a significant relation (Sjostrand C 2011), while other researches failed to confirm such relationship (Carter KN et al., 2005; Chang CL, Donaghy M, and Poulter N 1999; Schurks M et al., 2009).

Migraine not only linked to ischemic cerebral vascular lesions, but also linked to increase risk of cardiovascular diseases (CVD) (Ikeda K et al., 2005; Kurth T et al., 2009; Kurth T et al., 2016; Liew G, Wang JJ, and Mitchell P 2007; Vargas BB et al., 2008). Although the underlying etiology for the association between migraine and CVD remains unclear, many theories were postulated to explain this confirmed link, including shared genetics, environmental and comorbid factors like obesity, dyslipidemia and hypertension which are common in both migraine and CVD (Bigal ME et al., 2009).

Many studies tried to explore the connection between migraine and CVD. In one study significant reduction of the count and function of circulating endothelial progenitor cells (EPC) were noticed among migraine sufferers, compared to other headaches types. These cells prevent atherosclerosis by replacing the injured endothelial cells, so EPC abnormalities increase risk for CVD (Lee ST et al., 2008). Other studies revealed that migraneurs had dyslipidemia with diminished high density lipoprotein (HDL) and elevated low density lipoprotein (LDL) (Janoska M, Chorazka K, and Domitrz I 2015). Patients with migraine had higher levels of glucose and insulin with insulin resistance pattern (Wang X et al., 2017), not only that but also children with migraine and migraineurs without apparent CVD have a strong family history of early myocardial infarction or vascular events which rises the role of genetics (Bigal ME et al., 2009). Moreover, patent foramen oval (PFO) was observed in up to 40% to 60% of migraine sufferers especially MA and as MA also linked to platelet dysfunction, PFO May mediate passage of blood clots from right-to-left leading to myocardial or cerebral infractions (Finocchi C and Del SM 2015; Kumar P et al., 2019). But till now the link between migraine and CVD not fully understood, and whether all migraine types or specific migraine sub-types are linked with increased risk of CVD is still not confirmed.

Clinically, migraine is not restricted to the attacks of headaches, but includes a variety of other manifestations as autonomic nervous system (ANS) dysfunction, retinal, vascular and gastrointestinal symptoms (Campbell JK 1990). It is widely accepted that ANS dysfunction is one of the hallmarks of migraine, it occurs during and in between migraine attacks (Melek IM et al., 2007; Mosek A et al., 1999; Pogacnik T et al., 1993; Thomsen LL et al., 1995), however, the exact relationship between migraine and ANS is not clear and the researches in this field yielded inconclusive and conflicting results. Some studies postulated that migraine results from ANS dysfunction (Welch KM 1987), while others suggested that ANS dysfunction is a primary characteristic of migraine (Kuritzky A 1987), not only that but also the specific type of ANS dysfunction is not confirmed among migraineurs some studies found a

sympathetic hypo-activity among migraine sufferers (Peroutka SJ 2004), while others found a parasympathetic hypo-activity, some researchers detect sympathetic over activity and parasympathetic hypo-activity (Appel S et al., 1992) and others found over activity of both the sympathetic and parasympathetic systems (Yakinci C et al., 1999).

Cardiovascular system is controlled mainly by ANS, so ANS dysfunction may contribute to cardiovascular events among migraine sufferers. Cold pressor test (CPT) is a non-invasive autonomic test, used to assess the ANS function, mainly the sympathetic function. Cold temperature stimulates centrally mediated sympathetic system leading to peripheral vasoconstriction, and consequently increasing cardiac output and pulse so affect the heart rate (HR) and blood pressure (BP) (Richardson HL et al., 2013; Silverthorn DU and Michael J 2013).

The study aims was to evaluate sympathetic autonomic cardiovascular response to cold stress in migraine patients and compare it to control group.

2. SUBJECTS AND METHODS

The experiments were performed at the Neurology Department, Mouwasat Hospital, KSA throughout the period from May 2017 until May 2019. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Mouwasat Medical Hospital. Participation was voluntary; all participants gave their informed consent before enrolling in this research.

All participants were interviewed, full history taking was taken and complete neurological examination was performed by a senior neurologist. All participants had an unremarkable history except for migraine in patient group.

Inclusion criteria were the diagnosis of migraine based on International Headache Society's and welling to participate in this study. All patients had a repeated history of headache (at least five attacks), each attack of pulsating nature, lasting from 4-72 hours, either unilateral or bilateral, and was associated with nausea, vomiting, avoiding noises or bright lights, or both. Patients who had ever been experienced visual, speech, cutaneous sensation, or muscular disturbances were considered as migraine with aura (2013). The patients have "active migraine," which included patients with self reported migraine in the previous year and had at least one attack per month. The headache severity was evaluated using the standardized pain numerical rating scale from 0 to 10 where zero means no pain and 10 means maximum pain, also pain categorized into mild pain 1-3, moderate pain 4-6 and severe pain more than 7 (Jones KR et al., 2007).

Sixty-one consecutive patients (mean age of 28.42±3.85 years, 53 females and 8 males) were evaluated during the pain-free period; 38 patients have migraine without aura and 23 patients have migraine with aura. Patients were then compared to 30 age and sex matched control group (26 women and 4 men, with mean ages of 28.79±2.99 years). No one of the controls subject fulfilled the criteria of any primary headache (2013).

A complete history taking and neurological examination was performed by senior neurologist for all participants. All patients were evaluated by brain MRI to roll out the possibility of secondary headache. Any patient with abnormal neurological examination, abnormal brain MRI finding, perceive medications or had a systemic disease that might interfere with blood pressure or heart rate were excluded from the study.

Examination of the patient with migraine was under gone during a pain-free period (> 3 days after a pain attack). Each subject was asked to lie supine in a quiet room with an external accurate automatic upper arm blood pressure and pulse rate monitoring machine with Cuff 22-40cm, 120 Sets memory and LCD monitor (PARAMED). The machine was attached to one arm to measure blood pressure and heart rat while the other arm was immersed to just above the wrist for 5 minute in ice water at 4° C. Blood pressure and heart rate reading were obtained at 1, 3 and 5 minutes (Mitchell LA, MacDonald RA, and Brodie EE 2004; Roatta S et al., 1998; Silverthorn DU and Michael J 2013).

Data entry and analysis were performed using Windows IBM SPSS Statistics, Version 20.0. Armonk, NY: IBM Corp, 2011. The continuum was expressed in number and percentage. All data were presented as the mean value ± standard deviation (SD). The differences among various groups were determined by using Independent samples t-test (one-way analysis of variance). Simple linear regression test was used to detect the effect of disease duration on various parameters, statistical significance was determined at $p<0.05$.

3. RESULTS

This study was conducted on 91 participants, 61 of them fulfilled the diagnostic criteria of migraine based on International Headache Society classification and constitute the patient group, 86.9% of them were females (53 patents), their ages range from 23 to 41 years with mean ages of 28.42±3.85 years. The mean duration of the migraine was 7.95±3.27 years while the mean frequency of

migraine attacks per month was 4.80±1.51. The patient group was further subdivided into migraine with aura (23 patients) and migraine without aura (38 patients). Thirty participants constituted a control group, 86.7% of them were females (26 patients) with mean ages of 28.79±2.99 years (Table 1).

Table 1 Characteristics of the subjects

	Patients			Control
	M	MA	Total	
Number of subjects	38	23	61	30
Females percentage	86.8%	87%	86.9%	86.7%
Age (years)	29.22±3.93	27.10±3.39	28.42±3.85	28.79±2.99
Headache history (years)	7.30±3.22	9.02±3.14	7.95±3.27	-
Headache days/month	4.32±1.21	5.61±1.64	4.80±1.51	-
Headache intensity (0-10)	6.63±0.91	6.26±0.96	6.49±0.94	-

M= migraine without aura, MA= migraine with aura, Values are mean ± SD

When comparing the sympathetic cardiovascular response to cold temperature at baseline, after 2 minutes and 5 minutes there was a significant difference between patients and control group (Table 2), while there are no statistically significant differences between patient with and without aura (Table 3).

Table 2 Comparing the cardiovascular response to cold pressor in patient and control groups

CVS parameter	Patients	Controls	P Value
SBp 0 (mmHg)	120.05±7.89	125.13±6.36	P< 0.05
SBp 2 (mmHg)	135.87±8.00	142.40±7.27	P< 0.05
SBp 5 (mmHg)	127.18±7.02	131.50±5.83	P< 0.05
DBp 0 (mmHg)	78.03±4.73	73.77±2.56	P< 0.05
DBp 2 (mmHg)	92.21±3.74	89.57±3.80	P< 0.05
DBp 5 (mmHg)	84.20±3.77	85.90±3.76	P< 0.05
HR 0 (Beat/minute)	75.20±1.96	72.30±1.95	P< 0.05
HR 2 (Beat/minute)	86.26±2.49	83.40±2.19	P< 0.05
HR 5 (Beat/minute)	70.90±2.08	71.97±2.61	P< 0.05

CVS = cardiovascular system, SBp 0= systolic blood pressure at base line, SBp 2= systolic blood pressure after 2 minutes, SBp 5= systolic blood pressure after 5 minutes, DBp 0= diastolic blood pressure at base line, DBp 2= diastolic blood pressure after 2 minutes, DBp 5= diastolic blood pressure after 5 minutes, HR 0= heart rate at base line, HR 2= heart rate after 2 minutes, HR 5= heart rate after 5 minutes, P Value= statistically significant relation when P less than 0.05.

Table 3 comparing the cardiovascular response to cold temperature in patient with and without migraine

CVS parameter	M	MA	P Value
SBp 0 (mmHg)	119.58±7.39	120.83±8.76	0.55
SBp 2 (mmHg)	134.76±7.94	137.70±7.93	0.17
SBp 5 (mmHg)	126.87±7.21	127.70±6.81	0.66
DBp 0 (mmHg)	77.76±5.23	78.48±3.81	0.57
DBp 2 (mmHg)	92.05±4.17	92.48±2.98	0.67
DBp 5 (mmHg)	83.61±4.02	85.17±3.16	0.12
HR 0 (Beat/minute)	75.11±1.94	75.35±2.04	0.64
HR 2 (Beat/minute)	72.50±2.00	72.17±1.95	0.53
HR 5 (Beat/minute)	70.71±2.31	71.22±1.62	0.36

CVS = cardiovascular system, M= migraine without aura patients, MA= migraine with aura patients. Values are mean ± SD, SBp 0= systolic blood pressure at base line, SBp 2= systolic blood pressure after 2 minutes, SBp 5= systolic blood pressure after 5 minutes, DBp 0= diastolic blood pressure at base line, DBp 2= diastolic blood pressure after 2 minutes, DBp 5= diastolic blood pressure after

5 minutes, HR 0= heart rate at base line, HR 2= heart rate after 2 minutes, HR 5= heart rate after 5 minutes, P Value= statistically significant relation when P less than 0.05.

The mean systolic BP mmHg among patient group when compared to control group at baseline was 120.05±7.89 mmHg vs.125.13±6.36 mmHg (*P< 0.05*), after 2 minutes it was (135.87±8.00 mmHg vs. 142.40±7.27 mmHg (*P< 0.05*), while after 5 minutes it was 127.18±7.02 mmHg vs. 131.50±5.83 mmHg, *(P<0.05*). The mean Diastolic BP among migraine patients when compared to control group at baseline was 78.03±4.73 mmHg vs.73.77±2.56 mmHg (*P< 0.05*), after 2 minutes it was 92.21±3.74 mmHg vs. 89.57±3.80 mmHg (*P< 0.05*), while after 5 minutes it was (patients: 84.20±3.77 mmHg vs. controls: 85.90±3.76 mmHg, *P< 0.05*) (Table 2).

The mean HR beat/minute among patient group when compare to control group at baseline was 75.20±1.96 beat/minute vs. 72.30±1.95 beat/minute (*P<0.05*), after 2 minutes it was 86.26±2.49 beat/minute vs. 83.40±2.19 beat/minute (*P<0.05*) and after 5 minutes it was 70.90±2.08 beat/minute vs. 71.97±2.61 beat/minute (*P<0.05*) (Table 2).

In this study all migraine participants described their headache attacks as moderate or severe according to the standardized pain numerical rating scale. There was no statistically significant difference of the cardiovascular sympathetic response to cold temperature between migraineurs with moderate or severe attacks.

The mean systolic BP mmHg among migraine patients with moderate attaches when compare patients with severe attacks at baseline was 119.24±7.47 mmHg vs. 120.78±8.30 mmHg (*p*<0.73), after 2 minutes it was 134.62±7.65 mmHg vs. 137.00±8.27 mmHg (*p*<0.77), while after 5 minutes it was 126.14±6.94mmHg vs. 128.13±7.06 mmHg (*p*<0.75). The mean Diastolic BP among migraine patients with moderate attaches when compare patients with severe attacks at baseline was 77.62±4.67 mmHg vs. 78.41±4.82 mmHg, (*p*<0.99), after 2 minutes it was 91.62±3.98 mmHg vs. 92.75±3.49 mmHg (*p*<0.61), while after 5 minutes it was 84.03±3.93 mmHg vs. 84.34±3.67 mmHg *(p*<0.78) (Table 4).

Table 4 Effect of Headache severity on cardiovascular response to cold temperature in patients

CVS parameter	Moderate Headache	Severe Headache	P Value
SBp 0 (mmHg)	119.24±7.47	120.78±8.30	0.73
SBp 2 (mmHg)	134.62±7.65	137.00±8.27	0.77
SBp 5 (mmHg)	126.14±6.94	128.13±7.06	0.74
DBp 0 (mmHg)	77.62±4.67	78.41±4.82	0.99
DBp 2 (mmHg)	91.62±3.98	92.75±3.49	0.61
DBp 5 (mmHg)	84.03±3.93	84.34±3.67	0.78
HR 0 (Beat/minute)	75.10±2.09	75.28±1.87	0.48
HR 2 (Beat/minute)	72.10±1.68	72.63±2.20	0.13
HR 5 (Beat/minute)	70.97±1.97	70.84±2.20	0.68

CVS = cardiovascular system, M= migraine without aura patients, MA= migraine with aura patients. Values are mean ± SD, SBp 0= systolic blood pressure at base line, SBp 2= systolic blood pressure after 2 minutes, SBp 5= systolic blood pressure after 5 minutes, DBp 0= diastolic blood pressure at base line, DBp 2= diastolic blood pressure after 2 minutes, DBp 5= diastolic blood pressure after 5 minutes, HR 0= heart rate at base line, HR 2= heart rate after 2 minutes, HR 5= heart rate after 5 minutes, P Value= statistically significant relation when P less than 0.05.

The mean HR beat/minute among migraine patients with moderate attaches when compare patients with severe attacks at baseline was 75.10±2.09 beat/minute vs. 75.28±1.87 beat/minute (*p*<0.48), after 2 minutes it was 72.10±1.68 beat/minute vs. 72.63±2.20 beat/minute (*p*<0.13) and after 5 minutes it was 70.97±1.97 beat/minute vs. 70.84±2.20 beat/minute, *p*<0.68) (Table 4). Simple linear regression test was used to detect the effect of disease duration on the sympathetic cardiovascular response to cold temperature at baseline, after 2 minutes and 5 minutes. Figure 1 shows that there was a correlation between the duration of migraine and the systolic BP, the rises in systolic BP increase with increase in migraine duration (P<0.05). Figure 2 reveals the relation between diastolic BP and disease duration, patients with longer migraine showed higher diastolic BP compared with patients with

shorter disease duration (P<0.05). While; figure 3 show the relation between HR response to cold pressor test and disease duration, with higher hear rates in patients with longer disease duration (P<0.05).

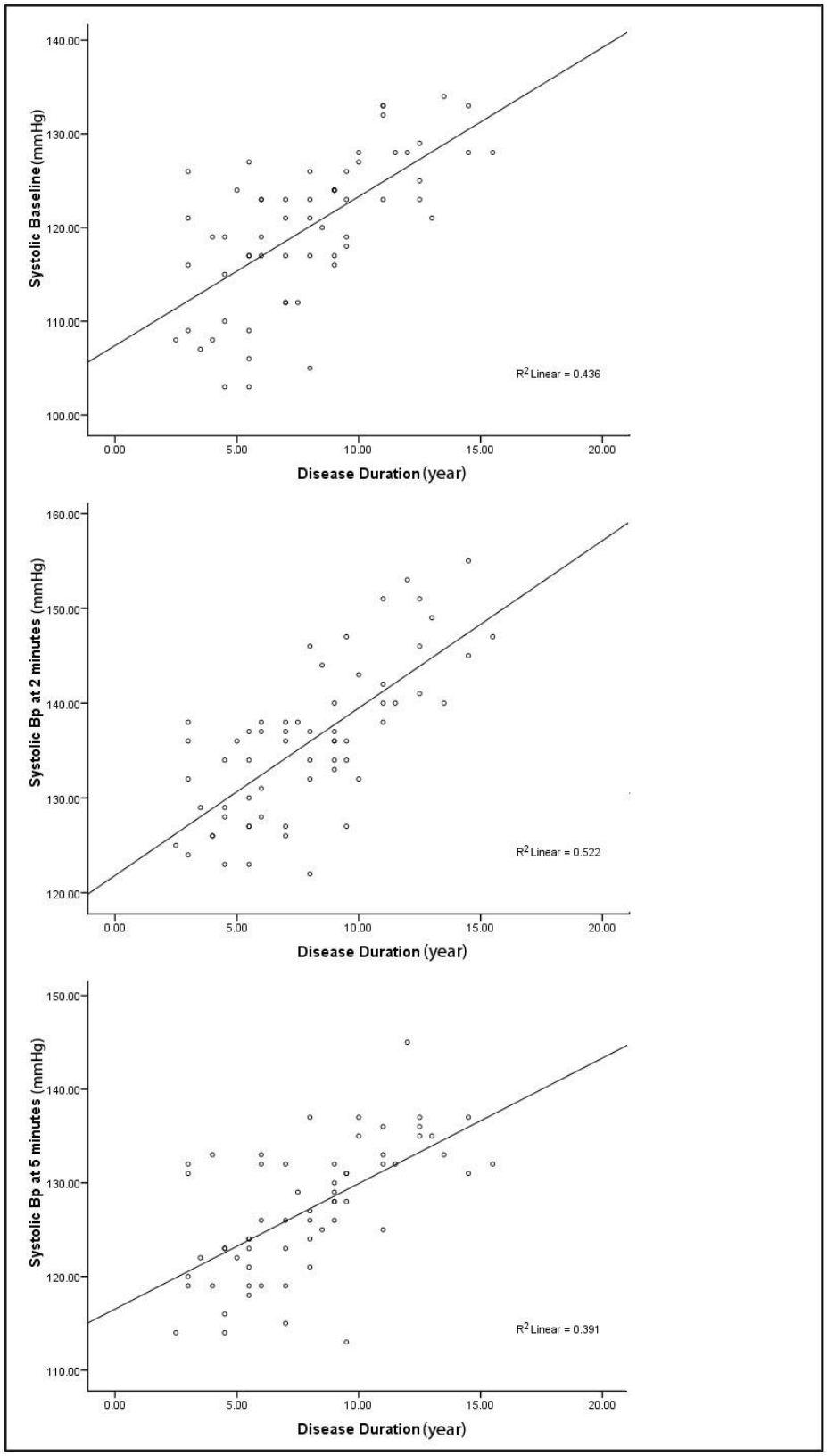

Figure 1 Systolic blood pressure response to cold presser test correlated to migraine duration.

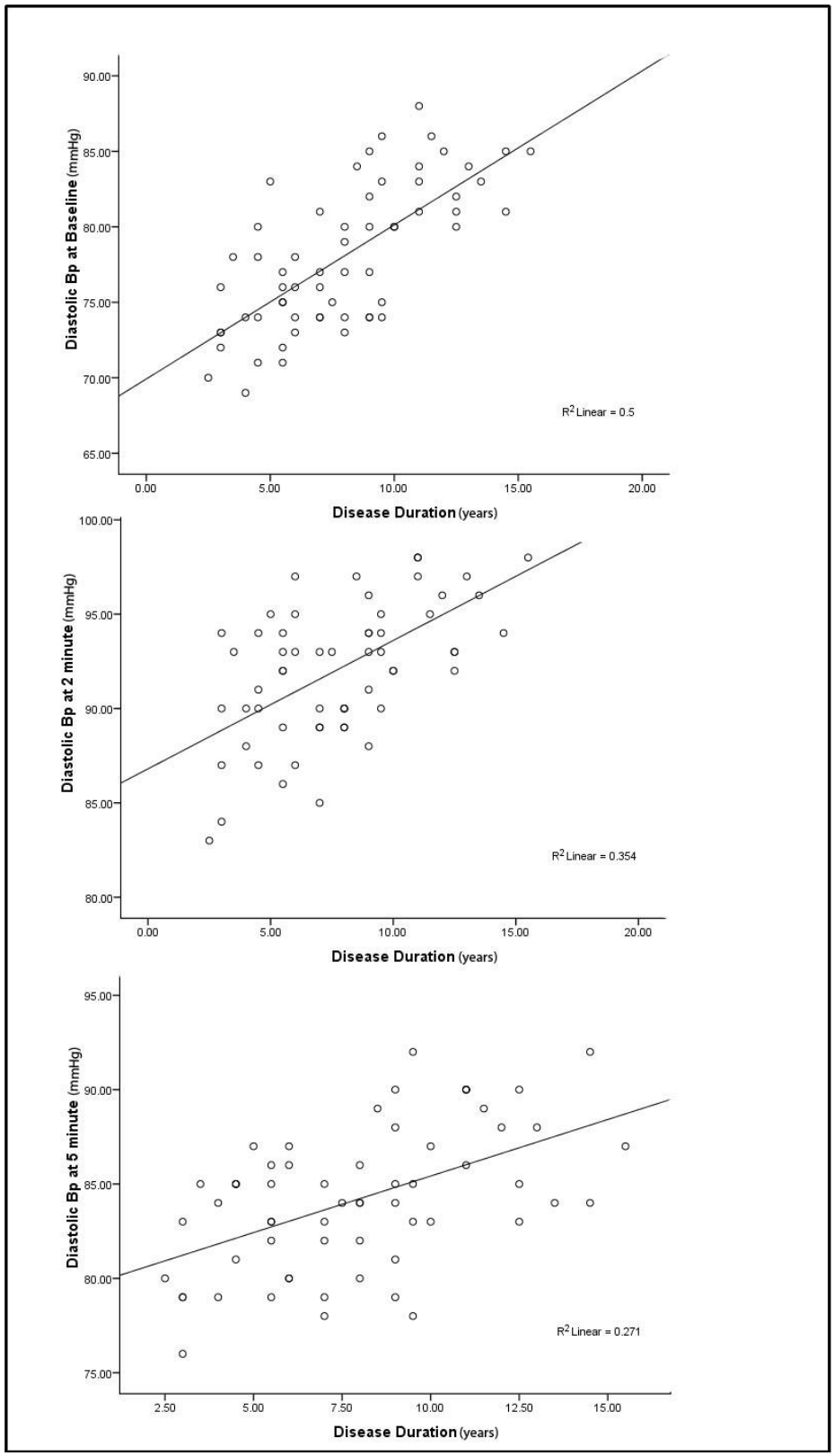

Figure 2 Diastolic blood pressure response to cold presser test correlated to migraine duration.

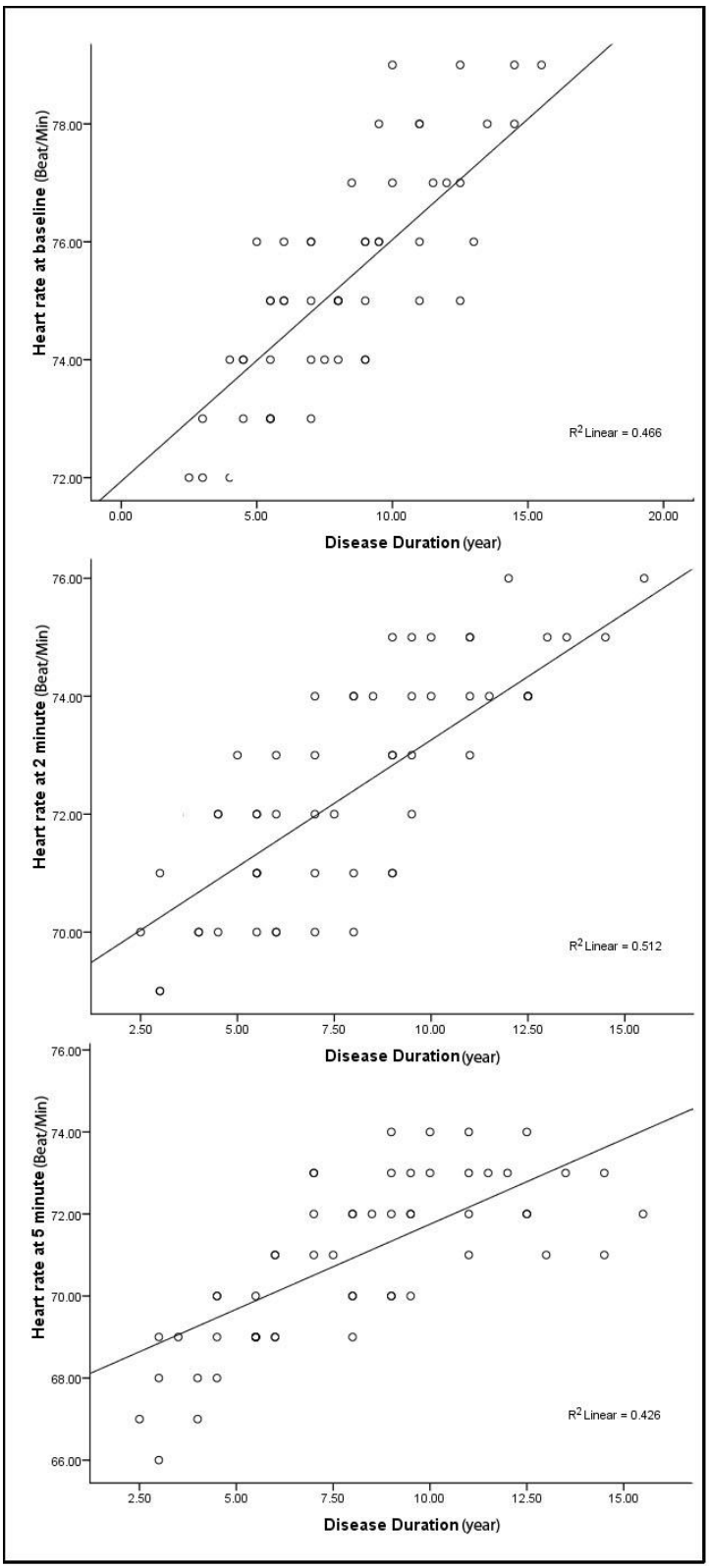

Figure 3 Heart rate response to cold presser test correlated to migraine duration.

4. DISCUSSION

Previously migraine was considered as a disease characterized by attacks of headache limiting the patient's daily activity and productivity, the main aim of management was to reduce the frequency and intensity of the migraine attacks. Nowadays a wider

view of migraine management was adopted by many clinicians, depending on the recent researches which revealed that migraine increases the risk of cerebrovascular accidents mainly cerebral ischemia (Buring JE et al., 1995; Etminan M et al., 2005; Gryglas A and Smigiel R 2017; Sacco S and Kurth T 2014) and increases the risk of CVD (Ikeda K et al., 2005; Kurth T et al., 2009; Kurth T et al., 2016; Liew G, Wang JJ, and Mitchell P 2007; Vargas BB et al., 2008). Many researchers linked migraine related CVD to autonomic dysfunctions, but they yielded conflicting results, some studies found decreased sympathetic functions (Peroutka SJ 2004), while others found decreased parasympathetic functions, others found over-activity of both the sympathetic and parasympathetic systems (Yakinci C et al., 1999), some studies found a sympathetic over-activity and parasympathetic hypo-activity (Appel S et al., 1992). The aim of this study is to evaluate sympathetic autonomic function among patients with migraine and compare it to controls using cold pressor test.

Our results analysis revealed that migraineurs are more responsive to cold temperature as stressor compared to controls. They showed elevated systolic and diastolic blood pressure as well as increased HR at rest, 2 minutes and 5 minutes after exposure to cold water, indicating that migraine patients have sympathetic hyperactivity even at rest. These results are in concordance with a research conducted by Matei et al., 2015, they concluded that migraineurs have sympathetic hyperactivity mainly at night and they found that sympathetic predominate the parasympathetic system in their studied group (Matei D et al., 2015).

The study of Aaron Shechter et al., 2002, found that resting diastolic, but not systolic, blood pressure was elevated in disabled migraineurs and they found that psychological stress or dose not affect blood pressure or HR. Also the research of Babayan et al., 2017, revealed vasomotor hyper reactivity among migraineurs. At 2008, Yerdelen et al., found that migraineurs have higher resting heart rate compared to controls, indicating sympathetic hyper activity but this difference was not statistically significant (Yerdelen D et al., 2008).

In contradictory to our results Havanka-Kanniainen et al., 1986, found no statistically significant differences in cardiovascular reflex responses among adult migraine patients and controls, they concluded that adult migraineurs have mild decrease in parasympathetic tone, but no definite decrease in sympathetic function (Havanka-Kanniainen H, Tolonen U, and Myllyla VV 1986), same results were obtained by Torun et al., 2013 (Torun E et al., 2013), and by Rauschel et al., 2015 (Rauschel V et al., 2015) Yoshida et al., 2017 in their study on adolescent migraineurs found that HR and systolic BP were not different between patients and controls, while Diastolic BP was significantly higher in patients in the supine but not in standing position, they concluded that adolescent migraineurs have significantly lower sympathetic vasomotor activity in the supine position and higher sympathetic vasomotor activity during standing (Yoshida S et al., 2017).

In this study, sympathetic cardiovascular response to cold stress was not significantly different between migraineurs with aura and migraine patients without aura; this is In agreement with the research conducted by Domingues et al., 2010, they also found there were no differences between patients with and without aura (Domingues RB et al., 2010), but we observed a direct correlation between migraine duration and sympathetic hyperactivity detected in patients group, while there were no correlation between severity of migraine attacks sympathetic over-activity.

5. CONCLUSION

Migraineurs have higher sympathetic tone compared to controls. Sympathetic hyperactivity is not significantly different between migraineurs with aura and without aura. A direct relationship between sympathetic over-activity and migraine duration was observed in patients group.

Ethics approval and consent to participate

The study protocol was approved by the ethical committee in Mouwasat Hospital, KSA, during the period from May 2017 until May 2019. Participation was voluntary and all contributors received detailed information about the aims of this research. An, we informed written consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

All raw data will be available on the editor request.

Competing interests

The authors declare that they have no competing interest

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Authors' contributions

All authors shared in this study design; they reviewed literature, and wrote the primary draft of the manuscript. All authors read and approved the final manuscript.

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