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Review Article

Linear heart rate variability measures in sickle cell disease compared to the healthy control subjects: a systematic review and mete-analysis study

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ABSTRACT

Introduction: Heart rate variability represents the performance of the cardiac autonomic nervous system (ANS) and is defined as the fluctuation of beat-to-beat between two successive R-waves (RR intervals). Accordingly, addressing the actions of the ANS in sickle cell disease helps in identifying the possible risk factors of sudden death. The clinical staging of the disease improves the diagnosis and the quality of the treatments.

Methods: This systematic review analyzed the data of the basal autonomic reactions in sickle cell anemia (SCA) and sickle cell trait (SCT) patients compared to healthy people. In this study, 441 articles were retrieved from PubMed, ProQuest, SCOPUS, Embase, and Web of Science databases. Some of them were removed based on the inclusion and exclusion criteria, and finally, seven articles remained for analysis.

Results: The data analysis of the included studies demonstrated that the vagal modulation at the basal condition decreased in SCA or SCT patients compared to the control group.

Conclusion: The sympathovagal balance was altered in SCA or SCT patients, and an increasing trend was observed in sympathetic nerve activities.

Keywords:
Heart rate variability
Sickle cell anemia
Sickle cell trait
Autonomic nervous system

Introduction

The autonomic nervous function has been demonstrated to be impaired in patients with different kinds of anemia such as vitamin B12 deficiency (Beitzke et al., 2002), iron deficiency (Yokusoglu et al., 2007) and thalassemia major (Kardelen et al., 2008). In fact, the autonomic nervous system (ANS) is the main regulator of human cardiovascular function to supply adequate blood flow (Michelini et al., 2015). Arterioles and venules are innervated by sympathetic neurons. The neuropathy and disturbance of these sympathetic fibers and sympathovagal balances cause vascular contraction, which is significantly affected by stress, emotion and pain. In addition, these factors have been reported in patients with sickle cell disease as the initiators of vascular occlusion crises (Chalacheva et al., 2017; Khaleel et al., 2017). Sickle cell anemia (SCA) is a genetic disease of the red blood cells and an autosomal recessive condition

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which contains different types. Patients who inherit copies of the mutant hemoglobin S gene from both parents experience the worst symptoms at a higher rate (Lonergan et al., 2001). Unlike SCA, a serious illness in which patients have two genes that cause the production of abnormal hemoglobin, individuals with sickle cell trait (SCT) carry only one defective gene. However, extreme conditions such as severe dehydration and high-intensity physical activity can lead to serious health issues including sudden death for individuals with SCT (Tsaras et al., 2009).

Although it has been shown that both SCA and SCT are associated with sudden death through a mechanism related to cardiovascular autonomic dysfunctions (Mestre et al., 1997), various documents report that these patients have no evidence in autopsy (Perronne et al., 2002). It seems that the autonomic impairment due to certain changes in the heart rate variability (HRV) could lead to a sudden death through a probable arrhythmia. The correlation between the clinical severities of sickle cell disease and the variability of the heart rate may provide new insight into understanding the mechanism of the crisis in the disorder to find new useful clinical approaches. According to some studies, sickle cell disease is a kind of anemia or trait that has been reported to be associated with autonomic dysfunction, acute chest pain, stroke, renal dysfunction (Quinn et al., 2005) and many cardiovascular disorders including cardiomegaly which occasionally lead to sudden death in patients (Bode-Thomas et al., 2011; Norris et al., 1991). Although different methods and tests have been identified as diagnostic tools for monitoring ANS dysfunction (Zygmunt and Stanczyk, 2010), in recent decades, measuring HRV as a simple non-invasive method for evaluating autonomic activity has obtained widespread interest (Camm et al., 1996). ANS dysfunction assessed by abnormalities in HRV is thought to play a role in the pathophysiology of sickle cell disease. It is suggested that changes in ANS may occur in patients with SCA during episodes of vaso-occlusive crises (Adebiyi et al., 2019). It is probably indicated that the altered immunity and inflammatory responses aggravated during vaso-occlusive crises might act as important factors in the pathophysiology of sudden death in patients with SCA (Adebiyi et al., 2019). The HRV refers to the fluctuations in the heart signals at the distance between two consecutive heartbeats. The heart rate is affected by the ANS, thus HRV parameters represent the function of the autonomic heart system. HRV measurement is a simple and non-invasive method that is widely used to examine the effects of sympathetic and parasympathetic activities on the heart (Camm et al., 1996). Although an SCA is basically a disease about the blood flow, the importance and involvement of the autonomic system in this disease at a steady-state condition have received less attention. Some controversies exist about the alteration of ANS activity in the basal condition in SCA (Sangkatumvong, 2011). Regarding the above-mentioned relations, focusing on the autonomic activity profile in SCA can create a deeper understanding of the etiology of the cardiovascular crisis and vascular occlusion which happen in this disease. Therefore, this systematic review aimed to pool data of basal autonomic reactions in SCA and SCT patients compared to healthy people.

Materials and methods

The applied method in this systematic review was recommended by the Centre for Reviews and Dissemination, York University. All methods of the research were consistent with the International Prospective Register of Systematic Reviews (PROSPERO). The protocol of this research was registered on 21/11/2018 with the PROSPERO (CRD42018115469) and https://www.crd.york.ac.uk (Supplementary S1. File). The employed methods in this systematic review are described in detail as follows.

Information sources and the strategy of the search

Several electronic bibliographic databases were searched from 22 to 31 December 2018, including PubMed, ProQuest, SCOPUS, Embase, and Web of Science. The terms of the applied search in each data basis for identifying studies regarding the aim of the research have been linked in a supplementary file (Supplementary S2. File). In addition, the reference lists of the selected articles/theses were hand-searched for finding possible relevant documentations. Medical subject headings and text words related to SCA and HRV were extracted and used in a search query in MEDLINE. The MEDLINE search strategy was used for other databases. Language and time restrictions were not applied in the meta-analysis. The search results from each database were exported to EndNote software and duplicate studies were deleted accordingly. The titles and/or abstracts of studies were

retrieved using the search strategy and those from additional sources were screened independently by two review authors to identify studies that potentially met the inclusion criteria. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by the same authors. Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third reviewer.

Eligibility criteria

Based on the inclusion criteria with regard to the languages and the type of the studies, full text English and non-English observational (descriptive, retrospective and prospective) and interventional (randomized controlled and quasi-controlled trials) studies were included without any time limitations.

The inclusion criteria regarding the characteristic of the subjects and the study

The subjects of the studies were patients (children and adults) with sickle cell disease regardless of the genotype and healthy control people. Furthermore, the time-domain HRV parameters (mRR: mean of RR intervals; SDNN: standard deviation of the inter-beat interval of normal sinus beats; pNN50: percentage of consecutive intervals differing from each other by more than 50ms; RMSDD: the root mean square of successive differences between normal heartbeats) were used based on the study aim. Other applied factors were frequency-domain HRV parameters (LF: low-frequency power; HF: high-frequency power; LF/HF ratio), measures of central tendency (mean and median), and indexes of dispersion (±SD, ±SE and interquartile range).

Exclusion criteria regarding the type of the study

Review articles, meta-analyses, single/series case reports, comments and meeting abstracts were excluded from the analysis.

Exclusion criteria regarding the characteristics of the subjects and the study

Studies with animal subjects, SCA patients being athletes, measuring the sympathetic nervous system activity by skin conductance, measuring sympathetic nervous system activity by cardiovascular autonomic tests such as the valsalva maneuver, squatting, tilt and deep breathing tests were excluded in this step. Other excluded studies were those reporting nonlinear HRV parameters, reporting HRV measurements in the form of percentage changes from baseline, and time and frequency-domain measurements not consistent with the task force's guidance.

Study selection

The titles and/or abstracts of the retrieved studies using the search strategy and those from additional sources were independently screened by two review authors to identify studies that potentially met the inclusion criteria. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by the same authors. Any disagreements between them over the eligibility of particular studies were resolved by discussion with the third reviewer. Finally, the eligible full text studies passing the inclusion criteria were also reviewed and selected with the same above-mentioned advisory method. In addition, the hand searching was conducted with the same advisory method to find additional related articles.

Data collection process and data items

All data related to the type of the study and the demographic characteristics of individuals were gathered according to the research question in the excel software. The participants' data (i.e., number, age and gender) and demographic characteristics (i.e., height, weight and body mass index) were extracted from the obtained studies. Additionally, information was provided on the genotypes of the patients and demographic characteristics of the comparator/control people. Data related to the daytime of record, duration of the recording, the position of the recording, breathing state, time-domain HRV parameters (i.e., mRR, SDNN, pNN50 and RMSDD) and frequency-domain HRV parameters (i.e., LF HF, and LF/HF ratio) were extracted as well.

Risk of bias in individual studies

Quality assessment was done using the NEWCASTLE-OTTAWA quality assessment scale, which considers the selection (case definition, representativeness of the cases, selection of controls and definition of controls), comparability (comparability of cases and controls based on the design or analysis) and exposure for retrospective studies. The quality assessment scale also considers the selection, comparability and outcomes

TABLE 1: Risk of bias assessment by NEWCASTLE - OTTAWA scale for included studies

Study (Year)	Selection (Max 5 stars)	Comparability (Max 2 stars)	Outcome (Max 3 stars)	Total stars acquisition	Quality of study	Risk of bias
Connes et al. (2006)	***	**	***	8	High	Low
Connes et al. (2008)	***	**	***	8	High	Low
Hedreville et al. (2008)	***	**	***	8	High	Low
Inamo et al. (2009)	****	*	***	8	High	Low
Nebor et al. (2011)	****	**	***	9	High	Low
Hedreville et al. (2014)	****	**	***	9	High	Low
Charlot et al. (2015)	****	**	***	9	High	Low

Acquisition of 8, 9 or 10 stars= High quality (low risk of bias); 5, 6 or 7 stars= Moderate quality (Moderate risk of bias); and 1, 2, 3 or 4 stars= Low quality (High risk of bias)

for cross-sectional and prospective studies. Two review authors independently assessed the quality of the included studies. Disagreements between the two authors over the quality assessment, in particular studies, were resolved by discussion with the involvement of a third review author where necessary (Peterson et al., 2011).

Data analysis

STATA (version 11) was used to analyze the data. The mean difference with a 95% confidence interval (95% CI) was applied as effect measures. In some studies, the mean and standard deviation were estimated from the median and the interquartile range and heterogeneity was assessed by I^2 values. The summary of mean differences was estimated by random and fixed effects models when I^2 values were ≥50% and < 50%, respectively (Wan et al., 2014).

Results

Characteristics of the included studies

Regarding the initial search, 441 articles were received based on the search process from PubMed (n= 67), Web of Science (n= 40), Scopus (n=149), Embase (n= 119) and ProQuest (n= 66). Then, the duplicates, animal studies, case reports, letters and studies investigating the heart rate but not its variability were removed from further investigations (n= 213). The remaining articles were screened based on titles and abstracts. Then, the full texts of thirty-one articles were reviewed for finding eligible articles while considering the inclusion/exclusion criteria. Some of them were excluded because of the lack of either performing other cardiac autonomic tests or analyzing standardized HRV measurements. Finally, seven articles were included in the meta-analysis (Figure 1). All the included studies had the same design and were observational reports. The quality of the selected studies and the risk of bias were assessed by a standard method, which confirmed the high quality of the articles with a low risk of bias (Peterson et al., 2011). In addition, the included studies were analyzed under random and fixed effects models (Borenstein et al., 2007). The included studies demonstrated a strong quality for review (Table 1) and were determined for age and gender in patients with SCT or disorder compared to a control group. Additionally, the parameters of linear HRV were investigated in the entire study. The detailed characteristics of the subjects of the included studies are described in Table 2. In addition, Table 3 provides the characteristics of the electrocardiogram recording and HRV analysis methods of the included studies.

HF, HFnu and LF/HF parameters of HRV in SCA or SCT

Out of seven studies, three papers reporting HF measures demonstrated significant differences between people with SCT and healthy people (I^2=41%, heterogeneity, P=0.183). Moreover, the meta-analysis of four studies showed significant effects in SCA group compared to

TABLE 2: Demographic characteristics of the subjects (SCA/SCT and Con) of the included studies.

Study (Year)	Number Male (Female) Total			Age (year) Mean SD			BMI (kg/m^2) Mean		
	SCT	SCA	Con	SCT	SCA	Con	SCT	SCA	Con
Connes et al. (2006)	-- (--) 9	--- ---	-- (--) 9	29.6 6.9	--- ---	27.8 4.2	23.72	---	24.32
Connes et al. (2008)	23 (0) 23	--- ---	17 (0) 17	24.1 1.4	--- ---	21 0.7	23.11	---	22.43
Hedreville et al. (2008)	7 (0) 7	--- ---	6 (0) 6	21.1 1.1	--- ---	19.5 0.5	22.49	---	23.34
Inamo et al. (2009)	--- ---	-- (--) 66	-- (--) 15	--- ---	NR	22.7 5.1	---	NR	NR
Nebor et al. (2011)	--- ---	14 (21) 35	13 (11) 24	--- ---	28.9 8.7	31.9 9.2	---	NR	NR
Hedreville et al. (2014)	--- ---	4 (3) 7	5 (4) 9	--- ---	33.3 10.8	34.8 8.4	---	21.07	25.44
Charlot et al. (2015)	--- ---	13 (9) 22	7 (8) 15	--- ---	15.1 2.3	14.3 2.9	---	18.60	18.70

SCA= Sickle cell anemia; SCT= Sickle cell trait; Con= control; SD= Standard deviation; BMI= Body mass index; NR= Not reported

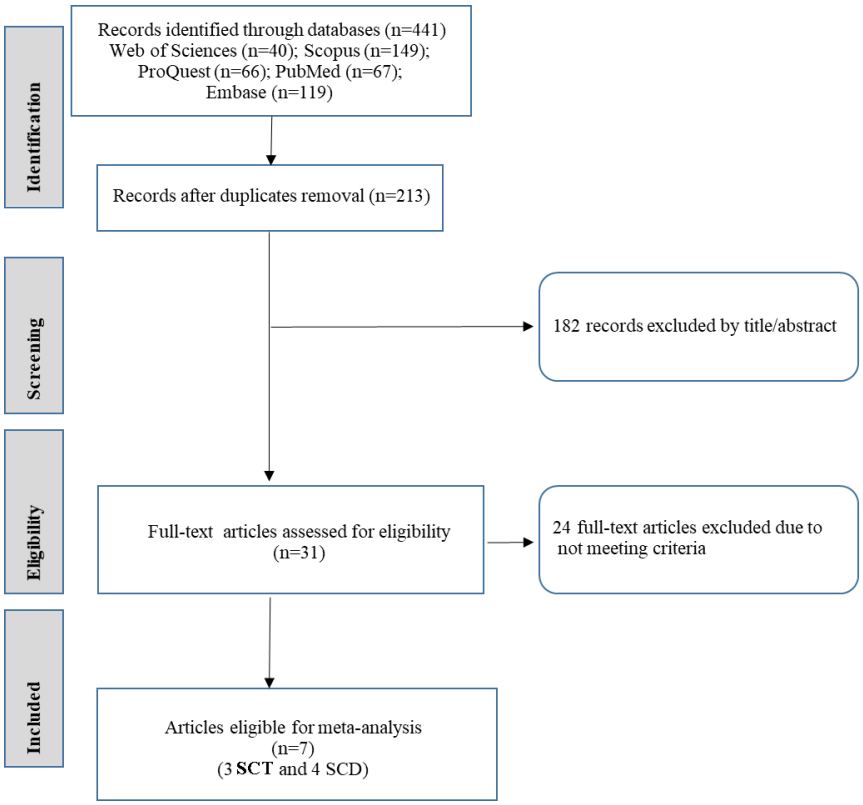

FIGURE 1. The chart of the search strategy for entering the papers in the meta-analysis.

the control group (I^2=93.1%, heterogeneity, P=0.000). In this part, there were significant effects between all patients with SCT or anemia and healthy control people with the overall heterogeneity of I^2=87.8% (P=0.000). Furthermore, meta-analysis indicated that lower HF demonstrated lower activity of the vagal nervous system in patients with SCT or anemia compared to healthy people in basic situations (Figure 2A).

The analysis further revealed that HFnu (an indicator of parasympathetic activity) was significant in SCT

TABLE 3: The Characteristics of the ECG recording and HRV parameters of included studies.

Study (Year)	ECG sampling rate (Hz)	Period of ECG recording	Period of analysis (min)	Position during record	Spectral analysis technique	Time domain HRV measures	Frequency domain HRV measures	Nonlinear HRV measures
Connes et al. (2006)	128	Long term (24 h)	Night (420)	Resting sleep position	FFT	mRR SDNN SDANN RMSSD PNN50%	VLFms^2 TPWms^2 LFms^2 HFms^2 LFnu HFnu LF/HF ratio	NR
Connes et al. (2008)	200	Long term (24 h)	Night (420)	Resting sleep position	FFT	mRR SDNN SDANN RMSSD PNN50%	VLFms^2 TPWms^2 LFms^2 HFms^2 LFnu HFnu LF/HF ratio	NR
Hedreville et al. (2008)	NR	Long term (24 h)	Night (420)	Resting sleep position	FFT	mRR SDNN SDANN RMSSD PNN50%	VLFms^2 TPWms^2 LFms^2 HFms^2 LFnu HFnu LF/HF ratio	NR
Inamo et al. (2009)	NR	Long term (24 h)	Night (420)	Resting sleep position	NR	mRR SDNN SDANN RMSSD -----	----- TPWms^2 LFms^2 HFms^2 ----- ----- LF/HF ratio	NR
Nebor et al. (2011)	NR	Long term (14 h)	Night (420)	Resting sleep position	NR	mRR SDNN ----- ----- -----	VLFms^2 TPWms^2 LFms^2 HFms^2 ----- ----- -----	NR
Hedreville et al. (2014)	NR	Long term (14 h)	Night (420)	Resting sleep position	FFT	----- SDNN ----- RMSSD -----	----- TPWms^2 LFms^2 HFms^2 ----- ----- LF/HF ratio	NR
Charlot et al. (2015)	NR	Short term (20 min)	Day (10)	Supine & Standing	FFT	mRR ----- ----- ----- -----	----- TPWms^2 LFms^2 HFms^2 ----- HFnu LF/HF ratio	NR

Electrocardiogram= ECG; HRV= heart rate variability; FFT= fast fourier transform; NR= not reported; HR= heart rate; mRR= mean of RR intervals; SDNN= Standard deviation of NN intervals; SDANN= Standard deviation of the 5 minute average NN intervals; RMSSD= Root mean square of successive RR interval differences; PNN50%= Percentage of successive RR intervals that differ by more than 50 ms; VLFms^2= Absolute power of the very-low-frequency band; TPWms2= Total power; LFms^2= Absolute power of the low-frequency band; HFms^2= Absolute power of the high-frequency band; LFnu= Relative power of the low-frequency band in normal units; HFnu= Relative power of the high-frequency band in normal units; LF/HF ratio= Ratio of LF to HF power

compared to the control group (I^2=0.0%, heterogeneity, *P*=0.847) while SCA represented no significant effect. Overall, HFnu had a meaningful effect between patients and the control group (I^2=32.5%, heterogeneity, *P*=0.217, Figure 2B).

The meta-analysis of data about LF/HF (a marker of autonomic nerves balance) demonstrated that patients with SCT had a higher value in comparison with

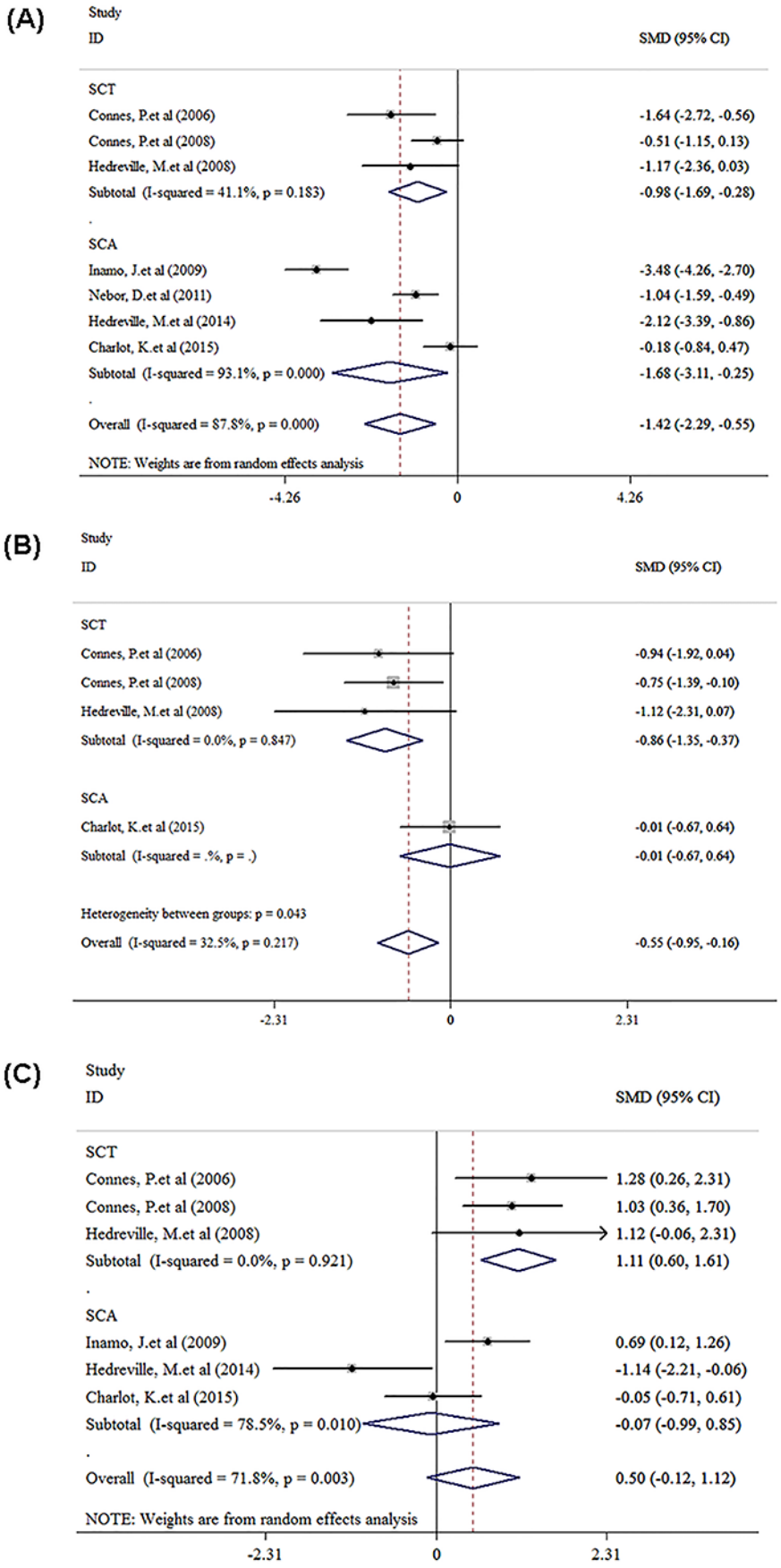

FIGURE 2. Effects of sesamol (50mg/kg) and exercise on net number of rotations in experimental groups upon a period of 30min. Data are expressed as mean±SEM. $^{***}P<0.001$ vs sham group; $^{\#}P<0.05$ vs 6-OHDA group.

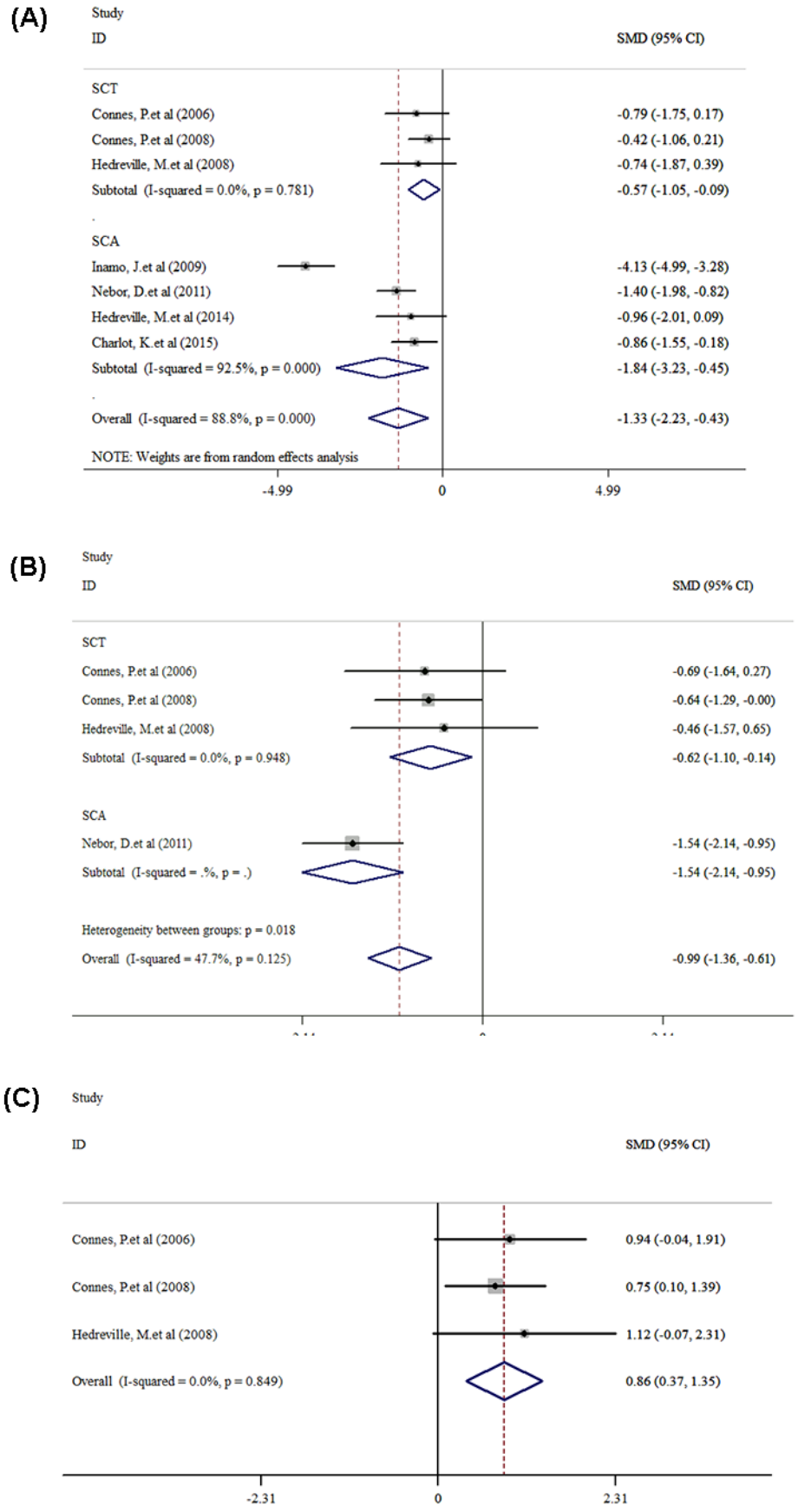

FIGURE 3. Frequency domain parameters of the heart rate variability. Forest plots show LF (A), VLF (B), LFnu (C) in SCT or SCA and all patients against heathy people. SMD: Standardized mean difference, ID: Identities of the included studies.

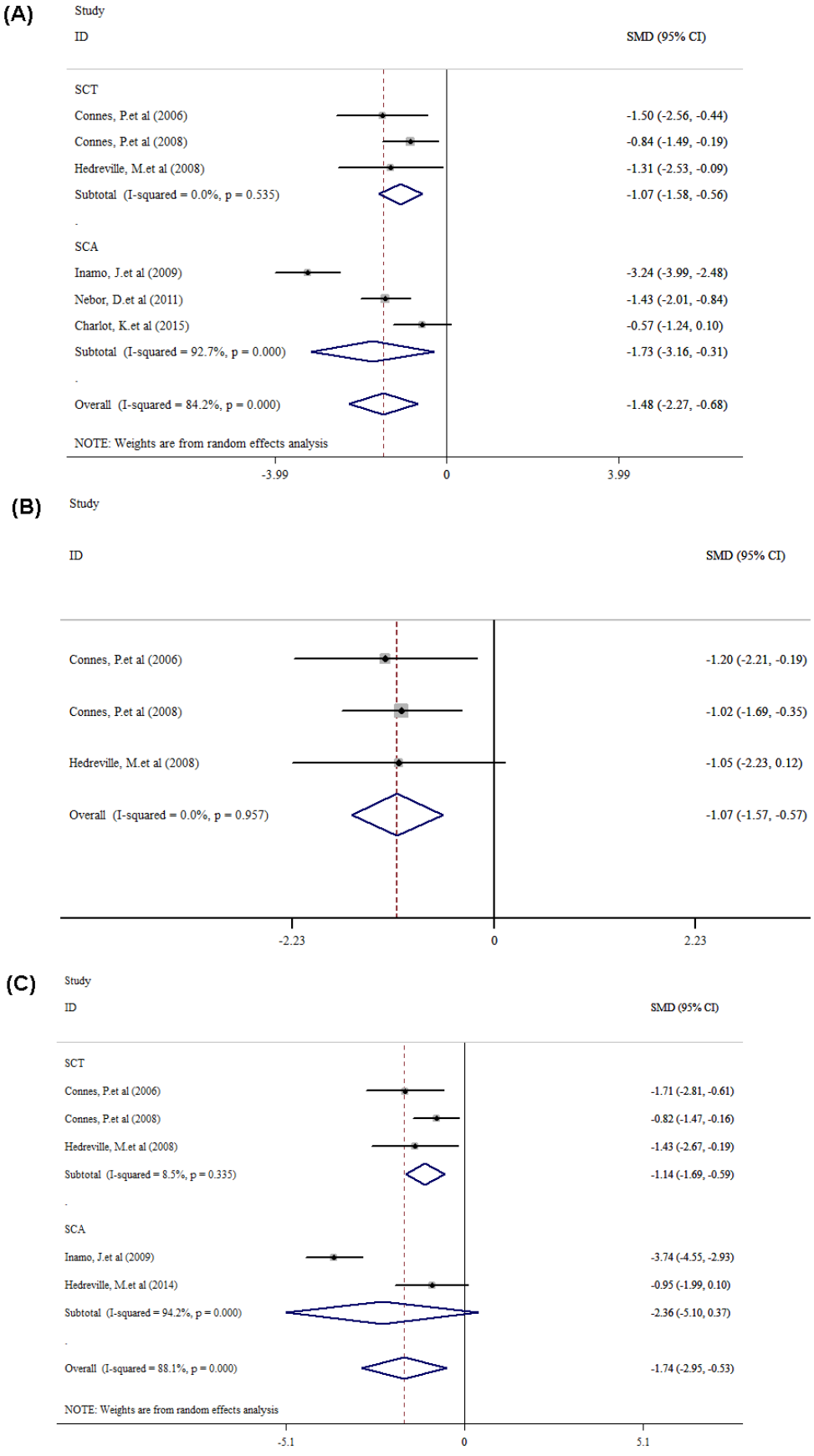

FIGURE 4. Time domain parameters of the heart rate variability (HRV). Forest plots represent mRR (A), PNN50 (B), RMSSD (C) in SCT or SCA and all patients versus healthy control people. SMD: Standardized mean difference, ID: Identities of the included studies.

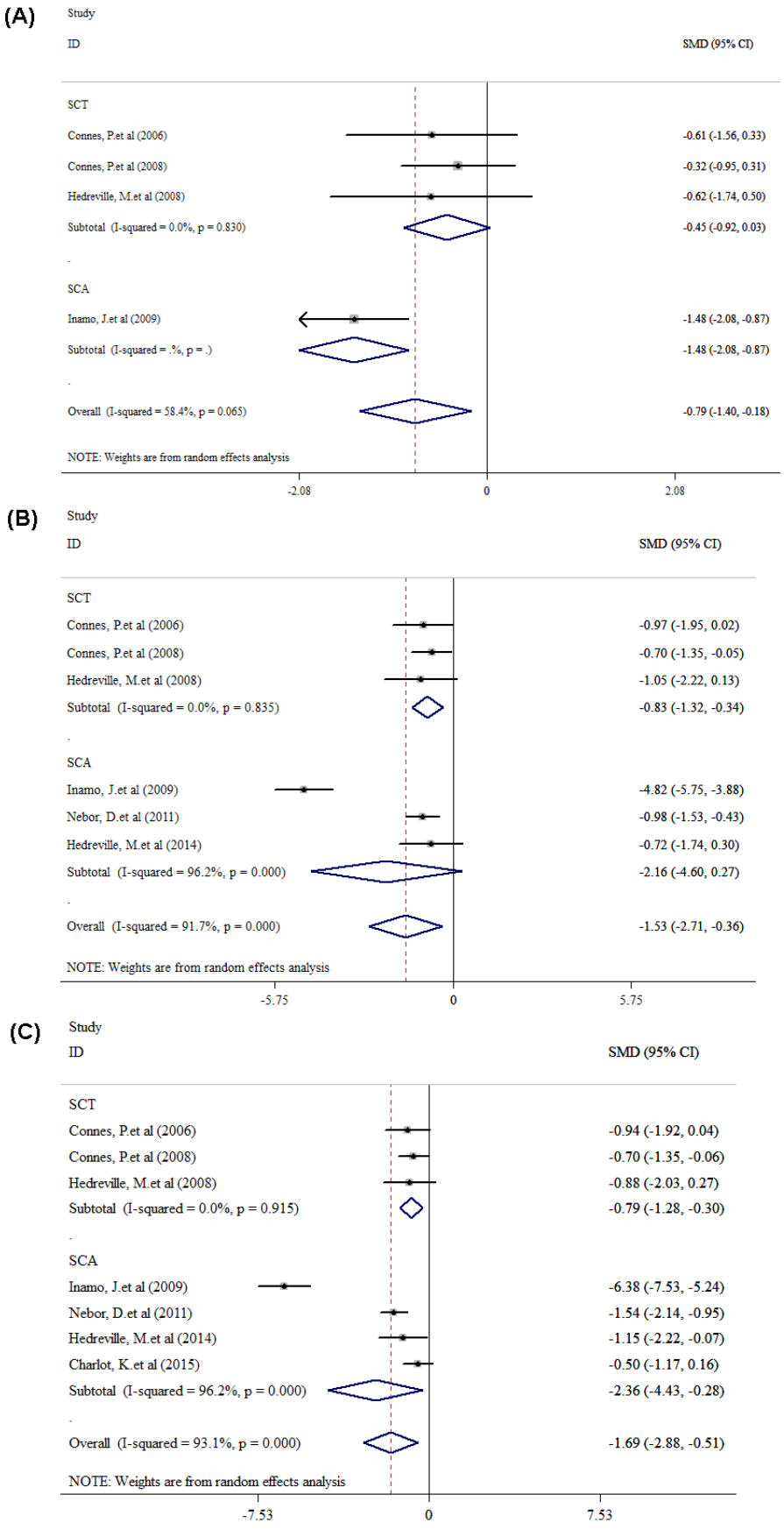

FIGURE 5. Parameters of the heart rate variability. Forest plots show SDANN (A), SDNN (B), TPWms2Hz (C) in SCT or SCA and all patients versus healthy control group. SMD: Standardized mean difference, ID: Identities of the included studies.

healthy people (I^2=0.0%, heterogeneity, P=0.921) while this parameter was not significant in SCA (I^2=78.5%, *P*=0.010). In general, no significant differences were observed between patients and healthy people (I^2=71.8%, heterogeneity, *P*=0.003) although there was an increasing trend in this regard (Figure 2C).

LF, VLF and LFnu parameters of HRV in SCA or SCT

Based on the meta-analysis of LF data, a meaningful effect was found in the SCT group compared to the control group (I^2=0.0%, heterogeneity, *P*=0.781). In addition, SCA patients represented a significant effect in comparison with the healthy group (I^2=92.5%, heterogeneity, *P*=0.000). The total data indicated that LF was significant in patients compared to healthy people (I^2=88.8%, heterogeneity, *P*=0.000, Figure 3A).

The data analysis of the VLF (an index of partially parasympathetic activity) showed a significant effect between SCT and the control group (I^2=0.0%, heterogeneity, *P*=0.948). Furthermore, a significant effect was detected between SCA and the control group. Overall, the analysis indicated a significant effect between patients and healthy people (I^2=47.7%, heterogeneity, *P*=0.125, Figure 3B). The obtained data demonstrated that the LFnu level was also significantly higher in patients compared to the control group (I^2=0.0%, heterogeneity, *P*= 0.849, Figure 3C).

MRR, PNN50 and RMSSD parameters of HRV in SCA or SCT

The meta-analysis of mRR results indicated that these parameters were significant in SCT patients compared to the control (I^2=0.0%, *P*=0.535). In addition, mRR measures were significant in SCA patients compared to the healthy control group (I^2=92.7%, *P*=0.000). Overall, the analysis confirmed significant effects in patients compared to healthy people (I^2=84.2%, *P*=0.000, Figure 4A). Based on the analysis of the time-domain measure of PNN50% (an index of parasympathetic activity), a significant effect was found in SCT patients in comparison to the control group (I^2=0.0%, *P*=0.957, Figure 4B). The analysis of the time parameter of RMSSD as a parasympathetic marker revealed a significant decrease in SCT (I^2=8.5%, *P*=0.335) while the data were not significant in SCA (I^2=94.2%, *P*=0.000). In general, this measure had a significant decrease in patients in comparison with the control group (I^2=88.1%, *P*=0.000, Figure 4C).

SDANN, SDNN and TPW parameters of HRV in SCT or disorder

The SDANN value as a marker of parasympathetic activity in SCT and SCA (all patients) had a lower level compared to the healthy control group (I^2=58.4%, *P*=0.065, Figure 5A). The SDNN level (as an index for global autonomic activity) in SCT had a significant decrease compared to the control group (I^2=0.0%, *P*=0.835) while the data analyses of the SDNN in SCA were not significant compared to healthy people (I^2=96.2%, *P*=0.000). The total analysis showed the significant effect in all patients compared to the control group (I^2=91.7%, *P*= 0.000, Figure 5B). The meta-analysis of the TPW data (a marker of global autonomic activity) revealed that SCT had a lower level in this parameter compared to control people (I^2=0.0%, *P*=0.915). Moreover, the levels of TPW were significant in SCA compared to healthy people (I^2=96.2%, *P*=0.000). Finally, the total analysis demonstrated a significant effect in patients in comparison to healthy people (I^2=93.1%, *P*=0.000, Figure 5C).

Discussion

Summary of evidence

Our meta-analysis in this research demonstrated alterations in the HRV and the baseline level of the autonomic nervous activity of the cardiovascular system in patients with sickle cell disease. In other words, it was found that the frequency parameters of HRV and the time-domain parameters changed in SCA or SCT. However, the major results of the present study indicated that patients with SCA or trait showed the depressed level of HF as a marker of vagal activity, which might be accompanied by cardiac autonomic neuropathy with the high risk of morbidity and mortality (de Andrade Martins et al., 2012; Mestre et al., 1997). In addition, the HFnu parameter of the HRV decreased in SCT carriers compared to control people. The observed results are consistent with those of several investigations showing the reduction of vagal activity in SCA or trait. For instance, was reported that patients with SCA demonstrated a significant reduction in parasympathetic responses following transient hypoxia in comparison with control subjects (Sangkatumvong et al., 2011). This study was excluded from the meta-analysis because the reported measures were expressed in terms of the percentage of the alteration from the baseline. In this line, there are

several outstanding studies which have been performed by a group of investigators whose works on the SCA patients revealed that different conditions such as transient hypoxia or spontaneous sighs could alter autonomic responses compared with normal subjects. Although the focuses of these studies were not on the baseline activities of autonomic nerves, the presentation of basal HRV parameters in the figures represented no changes regarding basal conditions in comparison with healthy subjects (Sangkatumvong et al., 2008a; Sangkatumvong et al., 2010; Sangkatumvong et al., 2008b; Sangkatumvong et al., 2011). Nonetheless, the current meta-analysis indicated that both parasympathetic nerve activities and sympathetic responses have been changed toward the vagal withdrawal and partial sympathetic dominancy at the basal situation. The observed effect size in the results of the HFnu parameter was also significant in SCT and a trend to decrease was found in SCA patients in comparison to the control, which was analyzed by a random statistical method indicating that the results of the total data significantly decreased in all patients.

The LF parameter, as a marker of sympathetic activity in these patients also decreased in both SCA and SCT. Conversely, the LF/HF ratio in SCT increased significantly and an increase was also observed in SCA, proving that the reduction in vagal activity was more prominent compared to the sympathetic alteration. These findings suggest that although sympathetic dysfunction, by decreasing in LF, complicated the balance of ANS in the sickle cell disorder, it should be noted that the vagal dysfunction has an outstanding role in the pathophysiology of sickle cell disease. Similarly, VLF decreased in all subjects (SCA and SCT) in comparison to heathy people. On the other hand, all the time-domain parameters of HRV such as mRR, PNN50, RMSSD, SDANN and SDNN showed a significant trend to decrease at the basal state, confirming frequency-domain results.

Taken together, the findings of this meta-analysis suggest that the ANS might play a significant role in the pathophysiology of the SCA or SCT which needs more investigations in the future in order to reveal the mechanistic correlations between them.

Autonomous nervous system in sickle cell disorder

The ANS dysfunction is involved in the pathophysiological mechanisms of the SCA and SCT. A low parasympathetic activity and sympatho-vagal imbalance in these patients might happen for adapting the cardiac system to compensate for the hemorrhagic condition in patients to keep adequate perfusion in tissues (Connes and Barthelemy, 2008). Furthermore, it was confirmed that increases in blood viscosity and autonomic dysfunction may increase vaso-occlusive painful crises (Connes and Coates, 2013). In addition, several mechanistic methods might be proposed for the clinical severity of the disorder which might lead to sudden death in these patients. These mechanisms may include the alteration of ANS responses of the cardiovascular system, changes in oxidative stress, pro-inflammatory cytokines, and nitric oxide bioavailability (Connes and Coates, 2013). It was hypothesized that the baseline ANS activity, which is changed in SCA, could alter pro-inflammatory cytokines in this disease, which is similar to what was reported in obstructive sleep apnea syndrome (Kim et al., 2011). Additionally, ANS reactivity in SCA patients differed compared with the control subjects following exposure to transient hypoxia (Sangkatumvong et al., 2010; Sangkatumvong et al., 2008b). In other words, repeated exposure to hypoxic situations in patients with SCA might destroy neuronal cells in the nucleus ambiguous which has sent plenty of vagal axons to the cardiac atria to regulate cardiac function (Ai et al., 2007). In spite of these vast issues, the precise mechanism underlying the alteration of ANS responses (parasympathetic withdrawal and increases in sympatho/vagal balance) is not clearly understood yet.

Increased cardiovascular risk in the SCA or SCT

Some cardiovascular adaptive responses (e.g., an increase in the heart rate and a decrease in the cardiac output) happened subsequent to myocardial dysfunctions and ischemia in sickle cell disease (Deymann and Goertz, 2003). In addition, some investigators reported several cardiac dysfunctions such as heart murmurs, ventricular hypertrophy and cardiomegaly (Assanasen et al., 2003; Batra et al., 2002) that might be accompanied by the risk of sudden death in SCA patients. Furthermore, ANS dysfunctions in SCA patients and SCT carriers were demonstrated in several cardiac autonomic tests beyond HRV measurements. Eventually, our meta-analysis confirmed that HRV measurements changed in these subjects probably due to the sudden death observed in this disorder.

Limitations

The heterogeneity of the results of the analysis was moderate to high for several reasons. Although the method and the type of the included studies were matched, the characteristics of the included subjects (e.g., age and gender) were different. In addition, the data analysis of the included studies was not performed with regard to gender differences, which might be the most important source of heterogeneity. Furthermore, the presence of more than one condition co-occurring with the main disorder or comorbidity might increase the number of the heterogeneity. The meta-analysis of the results of all participants showed some degree of heterogeneity due to the mixed SCA and SCT patients in the total statistical analysis.

One of the seven included papers measured the short-term parameters of HRV during the daytime while the other ones used the long-term HRV parameters in the night time. One study reported HRV measures as a median which statistically turned into a mean by software. These estimations made some degrees of heterogeneity in the total analysis. Finally, the number of the included patients was limited (n=264). To cope with this limitation, a random statistical method was used to calculate the effect size, which is a statistical method used in the case of large heterogeneity. Despite all the limitations, the meta-analysis was based on the results of several HRV parameters. Eventually, time-domain analyses confirmed the results of the frequency-domain findings.

Conclusion

Although most evidences reported that patients with SCT have normal lives without any serious complications, the results of the current meta-analysis indicated that the level of autonomic responses decreased in these patients (SCT) relative to healthy people. However, it was interestingly found that most of these HRV indices changed in both groups relative to healthy people. In general, the overall activity of autonomic responses in both SCT and SCA patients decreased by measuring by the HRV method. Although some indices such as HFnu and RMSSD changed only in SCT patients, most of them altered in both groups. Therefore, the overall activity of the cardiac autonomic system decreased in all patients. Finally, the findings of this study might help in identifying factors that worsen the subsequent crisis so that to diagnose the primary symptoms of the disease crisis and improve the quality of life of patients with sickle cell diseases.

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Conflict of interest

The authors declare that there is no conflict of interests.

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