



Autonomic tone modulation and night shift work: a prospective study in medical residents in Medellin, Colombia

Modulación de tono autonómico y trabajo en turno de noche: un estudio prospectivo en residentes médicos en Medellín, Colombia

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Keywords:

Heart rate variability,
autonomic tone,
Holter monitoring,
night shift,
arrhythmias.

Palabras clave:

Variabilidad de la
frecuencia cardiaca,
tono autonómico,
monitoreo Holter,
trabajo nocturno,
arritmias.

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Received:
15/10/2019

Accepted:
24/12/2019

ABSTRACT

Aim: To evaluate alterations in heart rate variability (HRV), repolarization, and cardiac rhythms in medical residents working night shifts in Medellín, Colombia, by using Holter monitoring as an indirect, non-invasive measure of autonomic tone. **Material and methods:** This was a descriptive, observational study, in which 48-hour Holter monitoring parameters were evaluated and compared in medical residents before, during, and after working night shifts. Data were analysed in four 12-hour periods: period 1: night before night shift or 24 to 12 hours before night shift initiation; period 2: day of night shift (12 hours before night shift initiation); period 3: during night shift work (12 shift hours); and period 4: 12 hours post-shift. A total of 52 residents of clinical and surgical residency programs were included in this study. Mean age was 28 years, 59.6% were female, and 77% were enrolled in public universities. A total of 45 hours of Holter monitoring data per resident were recorded and analysed. Heart rate variability decreased significantly ($p < 0.0001$) during period 2 (day of night shift), with an additional –yet less pronounced– decrease during period 3 (night shift work). **Conclusions:** Medical residents working the night shifts exhibited a decrease in HRV during periods 2 (before shift) and 3 (during shift), being more evident during period 2 (anticipatory phenomenon). This change in HRV is due to decreased in parasympathetic activity, however remaining within the normal range. Future additional studies are required in order to determine the long-term effects of HRV variation.

RESUMEN

Objetivo: Evaluar en residentes médicos que hacen turnos nocturnos la presencia de alteraciones en la variabilidad de la frecuencia cardiaca (HRV), repolarización y ritmo, a través de monitoreo Holter como medida no invasiva del tono autonómico en Medellín, Colombia. **Material y métodos:** Se realizó un estudio observacional, descriptivo, que evalúa y compara los parámetros del Holter antes, durante y después de la realización de los turnos nocturnos, en residentes de Medellín. Se dividieron las 48 horas en cuatro periodos: periodo 1 (noche anterior al turno o 24 horas antes del turno hasta 12 horas antes del turno); periodo 2 (día del turno o 12 horas antes del turno hasta iniciar el turno); periodo 3 (durante el turno o guardia o 12 horas del turno) y periodo 4 (12 horas post-turno). Se incluyeron 52 residentes con edad promedio de 28 años y 45 horas de registro. El 59.6% eran mujeres, 77% eran de universidad pública y se incluyeron áreas clínicas y quirúrgicas. La variabilidad de la frecuencia cardiaca se redujo significativamente ($p < 0.0001$) en el periodo 2, con una reducción adicional (menos pronunciada) al iniciar el turno (periodo 3). **Conclusiones:** Los residentes que realizan turnos nocturnos presentan reducción de la variabilidad de la frecuencia cardiaca durante los periodos 2 y 3, siendo más evidente en el periodo 2 (fenómeno de anticipación), este cambio en la variabilidad se debe a disminución de la actividad parasimpática, pero oscila dentro del rango de la normalidad. Se requieren más estudios para definir el impacto de estos hallazgos a largo plazo.

INTRODUCTION

Medical residents are general practitioners in training that are frequently subjected to 12-hour night shift work, classifying residents as a special population¹ assuming academic, administrative, and healthcare responsibilities in addition to social and family responsibilities. These circumstances may predispose residents to a greater risk of depression, stress, and burnout syndrome, among others.²

The human body is subjected to biological rhythms that vary with respect to the circadian rhythm, which is disrupted by sleep deprivation. The most frequent way circadian rhythm is disrupted by sleep deprivation is working night shifts (sleeping on average 2 to 4 hours less every day), which in addition has been associated to alterations in melatonin secretion, disruption of social relationships (social jetlag due to alterations biological clock and social life), and impacting the neuro-immune-endocrine axis. In this multi-causal context, these variations have been reported to be associated with an increased rate of cancer (especially breast cancer), diabetes, obesity, mood disorders, and macular degeneration.³ In addition, they have been associated with decreased heart rate variability, increased blood pressure (BP) and heart rate,⁴ as well as with increased secretion of catecholamines and cortisol, increased atherosclerosis predisposition or progression, and can thus be a potential risk factor for cardio-cerebrovascular disease.⁵

Heart rate variability (HRV) is a non-invasive measure used to identify alterations in the autonomic nervous system (sympathetic and parasympathetic), and can be measured by Holter monitoring.^{6,7} Under specific scenarios, HRV has been associated with increased cardiovascular mortality,⁸ post-myocardial infarction arrhythmias,^{7,9} compromised autonomic nervous system in diabetic patients,¹⁰ increased rate of sudden death after myocardial infarction,^{11,12} as a marker of brain death,¹³ uncontrolled arterial hypertension,¹⁴ overtraining syndrome in athletes,¹⁵ fibromyalgia,¹⁶ chronic fatigue syndrome,^{16,17} burnout syndrome,¹⁸ among others.¹⁹ Furthermore, HRV has also been used

to determine the effect of work-related stress and to establish the recovery of the same.²⁰

On the other hand, prolongation of the QTc interval –as an expression of the effect on repolarization in relation to autonomic imbalance– has been associated with increased cardiovascular mortality rates, mainly attributed to risk of lethal arrhythmias such as *torsades de pointes*,²¹ and coronary disease.²²

Therefore, by using Holter monitoring as an indirect, non-invasive measure of sympathetic and parasympathetic tone, in this study we have evaluated and assessed alterations in HRV, repolarization (by analysing QTc intervals), and cardiac rhythms in medical residents working the night shifts in the city of Medellín, Colombia.

MATERIAL AND METHODS

Study

This was a descriptive, observational study, in which Holter monitoring parameters were evaluated and compared before, during, and after working night shifts. All participants were medical (clinical and surgical) residents recruited by consecutive sampling from November 2017 to April 2018, and met the following inclusion criteria: age ≥ 18 years, provide signed informed consent, certify his/her position as a resident, having a night shift scheduled. Participants meeting the following criteria were excluded from the study: unwilling to participate; diagnosis of disease that required cardiovascular or metabolic management; having a cardiac stimulation device, personal history of cardiovascular disease, personal history of cardiovascular or neurovascular surgery, had a known arrhythmia –prior to Holter monitoring– that required treatment, arterial hypertension prior to Holter monitoring; cancellation of night shift; or participation in a different study.

Ethics

The Medical Ethical Committee at CES University approved this study. All participants provided signed informed consent to participate in this study. This study was performed complying with the Declaration of Helsinki.

Data

A survey that included demographic variables was administered to participating residents. Subsequently, participants were instructed on the operation of, and asked to wear a Holter monitor (DMS Service[®], model 300-3A) with 3 or 5 electrodes (3M[®], reference Red Dot™ 50 gel) for 48 hours.

Data recorded by the Holter monitor were analysed with CardioScan Premier software (DMS software, version 12.4.0054a). A team member who has a 20-year experience with this software analysed the data, and using this program, necessary filters were applied, and artefacts or background noise were eliminated in order to properly interpret our results. Holter data were analysed for the following four 12-hour periods: period 1: night before night shift or 24 to 12 hours before night shift initiation; period 2: day of night shift (12 hours before night shift initiation); period 3: during night shift work (12 shift hours); and period 4: 12 hours post-shift.

Period	Period 1	Period 2	Period 3	Period 4
Description	Previous night	Day of shift	Night shift work	Post-shift
Time relative to initiation of night shift	- 24 to -12 hr	-12 to 0 hr	0 to +12 hr	+12 to +24 hr

Results were blinded and independently read and interpreted by two trained co-investigators, and in case of discrepancies, a third a third co-investigator and a group consensus defined the case.

Statistical analysis

Data were tabulated in Excel, and statistical analysis was performed using SPSS software version 21 (licensed to CES University). Qualitative variables were shown as frequencies and percentages. Quantitative variables were represented as mean and standard deviation, or as median and interquartile range (IQR).

Bivariate analysis of categorical variables was performed using χ^2 test; and Student's t-test or Mann-Whitney U test were used to compare means, according to variables' distribution. Multivariate repeated measures analysis was performed, and Greenhouse-Geisser correction was applied to adjust the p value since the covariance matrix was non-spherical ($p < 0.05$). Tests for intra- and inter-subject effects were also analysed. Sample size was not calculated since previous estimates of prevalence of these alterations in similar populations are unavailable.

RESULTS

Residents of different programs including internal medicine, general surgery, obstetrics and gynaecology, paediatrics, emergency medicine, orthopaedics, neurosurgery, and anaesthesia, from four different universities in the city of Medellín that were scheduled for night shifts were recruited from November 1st, 2017 to April 30th 2018. A total of 104 residents were directly and indirectly invited to participate in this study, of which 52 were consecutively interviewed and included in our study. The remaining residents were excluded from the study due to unwillingness to participate ($n = 45$), personal history of cardiovascular ($n = 5$) or metabolic disease ($n = 2$). A total of 45 hours of data per resident were used for analysis.

Characteristics of the study population are shown in *Table 1*. Mean age of participants was 28 years; the majority was female, of mestizo race, and medium-high income level (according to Colombian standards), enrolled in public universities, in clinical residency programs (internal medicine, paediatrics), and currently on their first year of residency. Regarding scheduling, the frequency of programmed night shift work per day of the week was similar among our participants.

Results of Holter 48-hour monitoring data analysis are shown in *Table 2*. During the first period, 15.4% of participants exhibited decreased chronotropic response with scarce supraventricular and ventricular extrasystoles with arrhythmic load less than 0.1%. During the second period, 3.8% of participants presented a decrease in chronotropic response, 9.6% exhibited altered heart rate variability, and

one participant (1.9%) presented an episode of duplets, R-on-T, and ventricular bigeminy-trigeminy after a very stressful event (robbery),

and scarce supraventricular and ventricular extrasystoles with arrhythmic loads less than 0.1%. Similar results were observed for periods 3 and 4.

Table 1: Characteristics of study population.

Variable	Participants N = 52 (%)	
Age (years)	28.3 (18-37, SD 3.3)	
Sex	Female	31 (59.6)
	Male	21 (40.4)
Race	Mestizo	47 (90.4)
	Afro-Colombian	2 (3.8)
	White	3 (5.8)
Weight (kg)	65.6 (45-98, SD 12.00)	
Height (m)	1.67 (1.52-1.91, SD 0.09)	
BMI	23.4 (17.3-35.1, SD 3.17)	
Systolic BP (mmHg)	113.33 (90-140, SD 12.00)	
Diastolic BP (mmHg)	71.44 (50-98, SD 9.57)	
Heart rate (bpm)	78.8 (52-113, SD 9.8)	
Socio-economic level*	3	15 (28.8)
	4	11 (21.2)
	5	21 (40.4)
	6	5 (9.6)
University	Private	12 (23)
	Public	40 (77)
Medical specialty	Clinical	31 (59.6)
	Surgical	21 (40.4)
Service	Emergency Room	46 (88.5)
	Operating Room	3 (5.8)
	ICU	2 (3.8)
	Other	1 (1.9)
Hospital	Public	37 (71)
	Private	15 (29)
Year of residency	First	19 (36.5)
	Second	14 (26.9)
	Third	15 (28.8)
	Fourth	4 (7.8)
Day of night shift	Monday	7 (13.5)
	Tuesday	7 (13.5)
	Wednesday	9 (17.3)
	Thursday	10 (19.2)
	Friday	6 (11.5)
	Saturday	8 (15.4)
	Sunday	5 (9.6)

*Age, heart rate, weight, height, BMI (body mass index), systolic and diastolic blood pressure, rates per shift: absolute number represents the average (minimum-maximum, SD: standard deviation). Socio-economic level 3: (lower middle class); 4: (upper middle class); 5: (lower high class); and 6 (upper high class).

Table 2: Main findings of Holter 48-hour monitoring data analysis for each of the four 12-hour periods.

Holter Variable	Period 1 n (%)	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)
First-degree AV block	4 (7.7)	5 (9.6)	4 (7.7)	4 (7.7)
Second-degree AV block (Mobitz I)	2 (3.8)	1 (1.9)	3 (5.8)	1 (1.9)
Repolarization				
Normal	31 (59.6)	34 (65.4)	30 (57.7)	27 (51.9)
Early and/or T-wave alternans	21 (40.4)	18 (34.6)	22 (42.3)	25 (48.1)
Sinus bradycardia	50 (96.2)	48 (92.3)	47 (90.4)	50 (96.2)
Type 1 sinoatrial block		1 (1.9)	1 (1.9)	
Type 2 sinoatrial block	8 (15.4)	5 (9.6)	2 (3.8)	4 (7.7)
Tachycardia- insignificant pause-bradycardia pattern	4 (7.7)	6 (11.5)	4 (11.5)	8 (15.4)
Sinus tachycardia	49 (94.2)	49 (94.2)	47 (90.4)	50 (96.2)
Abnormal QT	4 (7.7)	4 (7.7)	3 (5.8)	3 (5.8)

Period 1: night before night shift or 24 to 12 hours before night shift initiation; period 2: day of night shift (12 hours before night shift initiation); period 3: during night shift work (12 shift hours); and period 4: 12 hours post-shift.

Two specific events were recorded: a prolonged QT interval upon awakening, and a case of idioventricular rhythm. Atrioventricular (AV) and sinoatrial (SA) conduction abnormalities were observed exclusively during periods of sleep, and were thus considered to be physiological events. Episodes of sinus tachycardia and bradycardia were always associated with the physiological phenomena of sleep-wake, physical activity, or activities in work areas. No clinical symptoms were recorded in the corresponding diaries of daily activities, nor silent or manifest ischemia.

The standard deviation of NN intervals (SDNN) is shown in *Figure 1A*. A statistically significant ($p < 0.0001$) reduction in SDNN was observed during period 2, with an additional yet less steep decline at time of night shift initiation (period 3). No significant differences in SDNN were observed between periods 2 and 3 ($p = 1$), or between periods 2 or 3 and 4 (post-shift day) ($p = 1$). Even though SDNN increased during period 4, the difference between periods 1 and 4 was statistically significant ($p = 0.004$). This effect was also observed when analysing intra- and inter-subject variability (*Table 3*).

When analysing by gender, we found that basal heart rate variability in males was greater than in females in all of the four analysed

periods (*Figure 1B*). Even though both male and female SDNN curves behaved similarly, and that changes in males were more pronounced than in females, both groups exhibited significant changes in heart rate variability, being the mean female SDNN 118.8 ms (CI 95% 108.15-129.49, $p = 0.015$), and 144.4 ms (CI 95% 128.07-160.85, $p = 0.0001$) in males.

Statistically significant differences in HRV were observed in participants enrolled in first (R1), second (R2), and third year of residency (R3), while no significant differences were observed for those in their fourth year (possibly due to a small R4 sample size) (*Figure 1C*).

Participants in R1 year exhibited mean SDNN values of 122.9 ms (CI 95% 105.98-139.87, $p = 0.05$); those in R2 126.0 ms (CI 95% 109.30-142.87, $p = 0.029$); R3 142.1 ms (CI 95% 121.81-162.38, $p = 0.009$), and R4 121.1 ms (CI 95% 63.75-178.61; $p = 0.567$). A phenomenon of anticipation, consisting of reduced heart rate variability during period 2 (i.e., between 7:00-19:00 h), was observed in all groups.

Regarding enrolment in private or public university, a similar behaviour was observed. Our data show that the greatest differences were found in R1 year residents, as well as those in R3 year, suggesting that adaptation

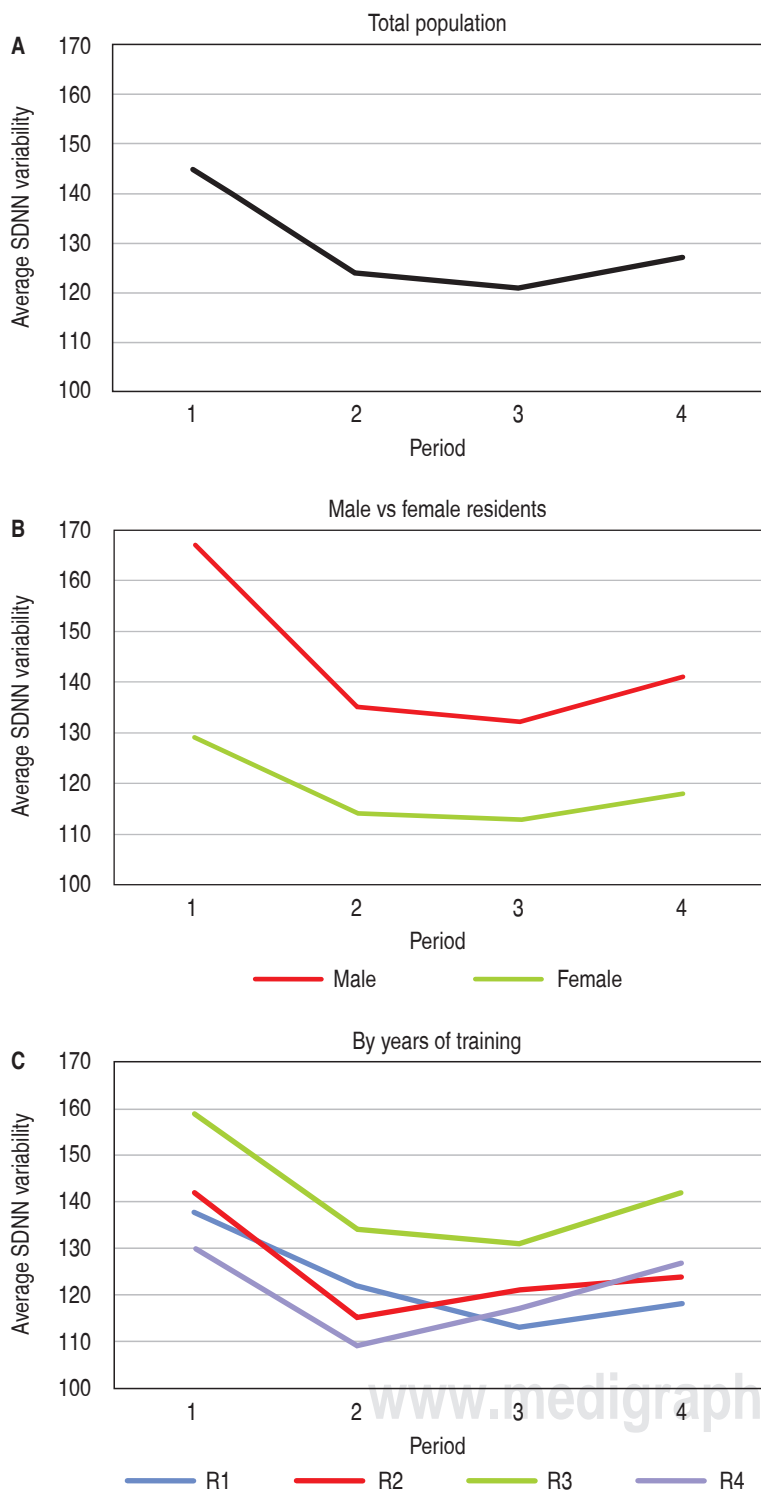


Figure 1: HRV evaluated through a time-domain measure: SDNN during the 48-hour period. Average HRV measured as SDNN for each of the four 12-hour periods is shown for: **A)** Total population, **B)** male vs. female residents, and **C)** by years of training (R1, R2, R3, R4).

to night shift work had not been completely achieved, contrasting with the improved period 3 variability observed in R2 and R4 residents. It should be noted that while the reduction in variability was statistically significant, it did not fall into abnormal levels.

Low frequency power (LF), high frequency power (HF), and LF/HF ratio exhibited different patterns (Figure 2). In all 4 periods, LF power did not show statistically significant intra-subject differences (intra-subject variability among 4 periods; Pillai’s Trace test: $p = 0.15$). However, significant inter-subject differences were observed (inter subject variability against another during the 4 periods: $p < 0.0001$), mean 1,151.17 (CI 95% 966.71-1,365.63). Pairwise comparison (comparison of variability differences between different periods) did not show any statistically significant differences between periods 1 and periods 2, 3, and 4, suggesting that the sympathetic system was active and did not exhibit changes in its activation mode during the recorded 48 hours.

On the other hand, analysis of high frequency (HF) power showed significant intra-subject (Pillai’s Trace test $p \leq 0.0001$) and inter-subject ($p \leq 0.0001$, mean 541.0 CI 95% % 397.27-684.74) differences. In addition, pairwise comparison showed a statistically significant difference between periods 1 and 2 ($p < 0.0001$, mean difference 222.66, CI 95% 80.47-364.86), suggesting that the sympathetic system was active during the night previous to the work shift, and that during period 2 (day of night shift), there was a decrease in the parasympathetic influx, which was recovered in periods 3 and 4. These findings may partly explain our findings of a lower HRV for period 2, which was more evident in R2 and R4 residents, while HRV in R1 and R3 residents was, in fact, lower.

Analysis of LF/HF ratio showed statistically significant intra-subject ($p \leq 0.0001$) and inter-subject differences ($p \leq 0.000$, mean 2.82, CI 95% 2.49-3.15). Pairwise comparison showed statistically significant differences between period 1 and periods 2 and 3 (day of night shift, $p < 0.0001$). However, there were no significant differences when comparing periods 1 and 4 (post-shift, $p = 0.5$), or periods 2 and 3 ($p = 1$).

It is worth to point out that in Figure 2, a mirror image of HRV can be observed, and

Table 3: Comparison of variability by subject and by peers.

By subject					
		Average	Standard deviation	Confidence interval 95%	
HRV SDNN (ms)	Period 1	144.90	42.2	133.13	156.67
	Period 2	123.06	42.9	111.09	135.022
	Period 3	121.13	35.1	111.35	130.91
	Period 4	127.62	40.8	116.25	138.97
By peers					
Period	Difference of averages	Statistical significance		Confidence interval 95%	
		p-value			
Period 1 (Ref.)					
Period 2	21.84	< 0.0001		7.90	35.7
Period 3	23.76	< 0.0001		12.52	35.0
Period 4	17.28	0.004		4.06	30.51

a predominance of the sympathetic over the parasympathetic tone is evidenced on the day of the shift (day and night). Once again an anticipation pattern is observed, in which knowing which is the day of the shift, and not going to the shift itself, leads to the activation of the sympathetic system without significant HRV variation, while the parasympathetic activity is reduced 12 hours before the shift (period 2). It is remarkable, however, that sympathetic activity is still predominant despite that residents sleep during the hours prior to the shift.

The percentage of successive normal sinus RR intervals > 50 ms (pNN50%) showed results similar to those of HF power (Figure 3), which is expected since they similarly estimate sympathetic tone. Statistically significant intra-subject differences were identified in all four periods ($p < 0.0001$), as well as inter-subjects ($p \leq 0.0001$, mean 15.17 %, CI 95% 12.42-17.93).

Similarly, pairwise comparison showed statistically significant differences between period 1 and periods 2 ($p \leq 0.0001$) and 3 ($p = 0.002$), being greatest the difference observed with period 2 (07:00-19:00 h, day of night shift) than with period 3 (19:00-07:00 h night shift or on-call). On the other hand, no significant statistical difference was identified between period 1 and 4 ($p = 0.34$).

DISCUSSION

The impact of shift work or on-call duty on the autonomic nervous system in medical and paramedical personnel has been frequently assessed by analysis of HRV. However, similar studies in staff in training are scarce. Therefore, in this study we have evaluated and assessed alterations in HRV, repolarization (by analysing QTc intervals), and cardiac rhythms in medical residents working 12-hour night shifts in the city of Medellin, Colombia.

Our results showed greater differences in HRV, SDNN, HF power, as well as in pNN50% during the day of the shift (period 2; 12 hours prior to shift initiation, 07:00 to 19:00 h), and not during the night shift itself.

Nonetheless, further future analyses are required since despite a statistically significant difference in HRV, the decreased values did not reach levels considered to be abnormal in other clinical settings (e.g., post-myocardial infarction). In addition, the response pattern suggests an anticipation reaction, which can be ontologically explained by the evolutionary adaptation of the autonomous nervous system to stress.

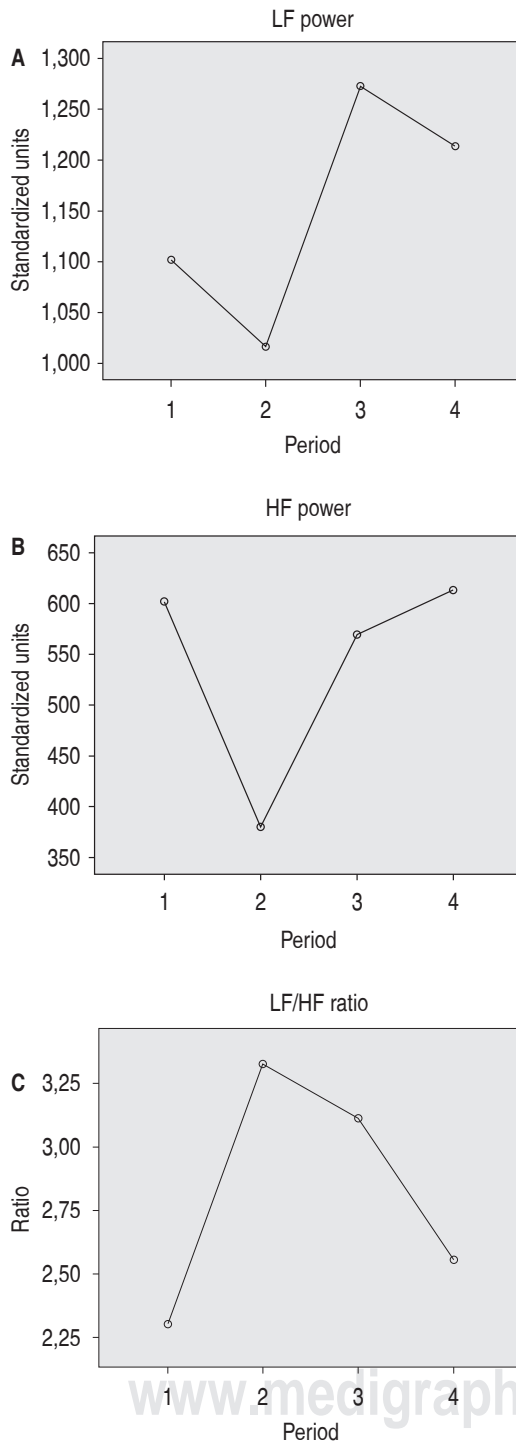


Figure 2: HRV evaluated through frequency-domain measures: LF, HF, and LF/HF ratio during the 48-hour period. Average HRV measured as **A)** LF, **B)** HF, and **C)** LF/HF ratio is shown for each of the four 12-hour periods.

A recent study in a population of medical residents found that first-year residents were exposed to low and high strain jobs with little control, greater stress, and alterations in HRV, suggesting sympathetic-parasympathetic tone imbalance.²³ In addition, an exploratory study of stress measurement in surgical population evidenced that HRV was more altered before the surgical procedure than during the actual procedure itself, thus suggesting an anticipatory phenomenon.^{24,25} A similar event was reported in anaesthesiology residents working the night shift,²⁶ strongly suggesting that the greatest drop in HRV is due to decreased parasympathetic activity together with an anticipatory event in the moments prior to starting the night shift. Our data showed that in the second and fourth years of residency, despite of presenting an anticipatory event, there was an improvement in HRV during the night shifts (perhaps an adaptation phenomenon?). Additionally, studies in surgeons show that HRV parameters improve during the night shift.²⁷

Several studies in personnel of different specialties showed decreased parasympathetic tone prior to night shift initiation, however, there is a discrepancy with other studies in which an improvement in parasympathetic tone during and after night shifts was reported.²⁸⁻³¹ However, the long-term implications of alterations in HRV in this population –medical residents– have

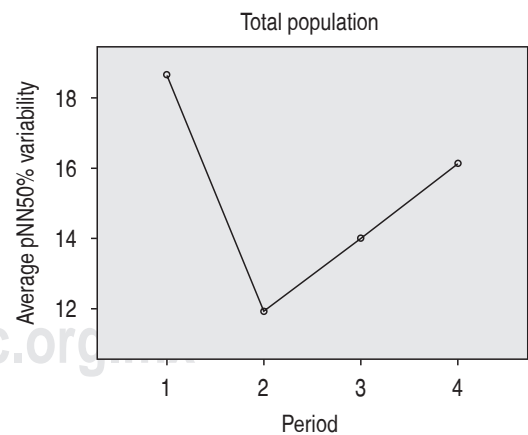


Figure 3: HRV evaluated through a time-domain measure: pNN50% during the 48-hour period. Average heart rate variability measured as pNN50% is shown for each of the four 12-hour periods.

not been established. Moreover, the effects of anticipatory events, and how to achieve faster an adaptation event (taking into account that many of the observed changes did not reach the pathologic threshold, $SDNN < 70$ ms) remain to be determined.

Throughout the literature, several long-term associations of changes in HRV with adverse outcomes have been reported in staff working the night shift and on on-call duty. A prospective study in nursing personnel showed that those women working more night shifts (at least 3 night shifts per month) were at a higher risk of cardiovascular disease (CVD), and even more so if they had worked more than five years with rotating night shifts (HR 1.17, CI 1.01-1.36 for 10 years and HR 1.29, CI 1.08-1.54 for 5-9 years).²⁸ On the other hand, another study in nursing personnel reported no significant differences between nurses working day shifts compared to those working night shifts. However, in that study, an increased risk of CVD was identified for those participants reporting insomnia (OR 3.07, CI 1.30-7.24), regardless of whether they worked the night shift.²⁹ Furthermore, additional reports have shown higher rates of diabetes, dementia, and CVD mortality in healthcare personnel working the night shifts,³⁰ as well as a higher probability of making mistakes and causing accidents.³¹

Studies in other healthcare professions have provided evidence to suggest that night shift work may favour the development of a chronic disease risk profile, especially for CVD.^{31,32} Medical personnel working night shifts also exhibits higher risk of CVD, increased rate of arrhythmias (increase of ventricular extrasystoles), and an increased LF power of the frequency domain, which speaks of sympathetic tone.³³ Alterations of the autonomic nervous system, expressed as measures of HRV, have also been associated with stress at the workplace and emotions of irritation, feeling of stress, and satisfaction.²⁰ Furthermore, alterations in HRV parameters in night shift workers have been also reported when the same activity that is performed during the day is performed during the night shift, which may be associated with diminished alertness that may lead to errors and accidents.³⁴ A loss of heart rate variability or decreased vagal tone have been associated to mild hypertension.³⁵

The study limitations include the non-random assignment in the study design; the convenience sampling, and that data are limited to 48 hours pre-, during, and post-night shift of only one shift per participating resident. Nonetheless, our study has strengths including the participation of clinical and surgical residents, as well as participation of public and private hospitals.

CONCLUSIONS

Medical residents working the night shifts exhibit changes in HRV, as evidenced by decreased time and frequency domains during periods 2 (before shift) and 3 (during shift), being more evident during period 2 (anticipatory phenomenon). This change in HRV is due to decreased in parasympathetic activity, however remaining within the normal range.

No clinically significant arrhythmias or alterations in QTc interval were identified, except in 3 specific cases (bigeminy-trigeminy with R-on-T, slow ventricular tachycardia, and prolonged QTc upon awakening).

Our findings are consistent with previous studies throughout the literature, however future complimentary studies are needed in order to determine any long-term effects of HRV variation.

FUNDING

This study was funded by *Cardiología* CES and by a CES University "Mínima Cuantía" grant.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. Gerardo Guio for his logistic support by kindly providing the Holter monitors used in this study.

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