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2019

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- Electrocardiographic abnormalities in subarachnoid hemorrhage
- Hands-only cardiopulmonary resuscitation and public access defibrillation
- Clinical vs statistical significance
- Abnormal origin of the right pulmonary artery from the aorta

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Original Research

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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

Helber Gonzalo López-Patiño,* César Daniel Niño-Pulido,*
Elsa María Vásquez-Trespalacios,‡ Julián Miguel Aristizábal-Aristizábal,*
Mauricio Duque-Ramírez*

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.

ABSTRACT

Aim: To evaluate alterations in hear rate variability (HRV), repolarization, and cardiac rhythms in medical residents working night shifts in Medellin, 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. At 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.*

* Department of Electrophysiology and CES Cardiology at CES University, Medellín, Colombia. Clínica Las Américas, Medellín, Colombia.
‡ Department of Epidemiology at CES University, Medellín, Colombia.

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INTRODUCTION

Medical residents are general practitioners in training that are frequently subjected to 12-hour night shift work, classifying residents as a special population[1] 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 Medellin, 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 of 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 Medellin 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

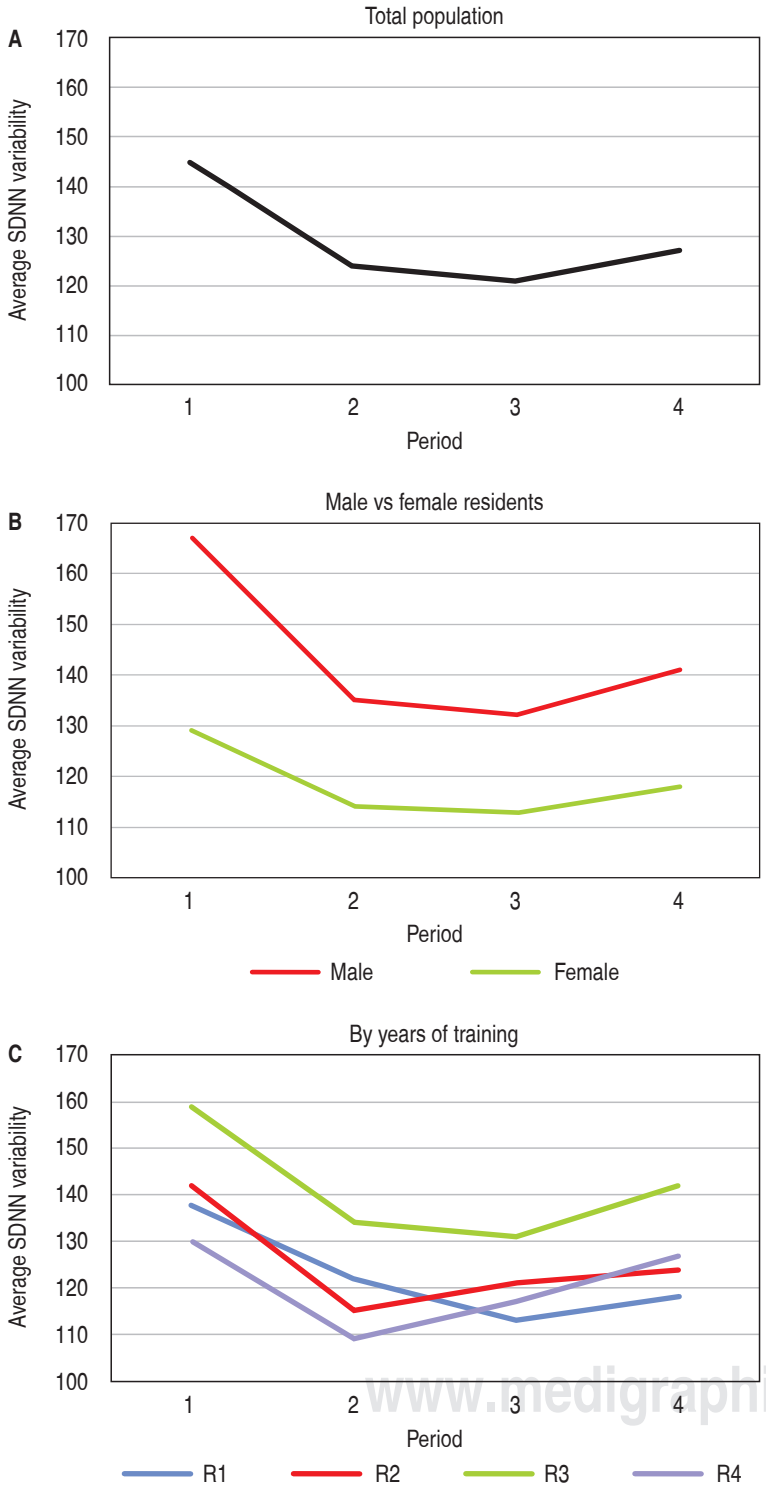

Figure 1: HRV evaluated through a time-domain measure: SDNN during the 48-hour period. Average HRV measured as SDNN for each of the four 12-hour periods is shown for: **A)** Total population, **B)** male vs. female residents, and **C)** by years of training (R1, R2, R3, R4).

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 p-value	Confidence interval 95%	
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.

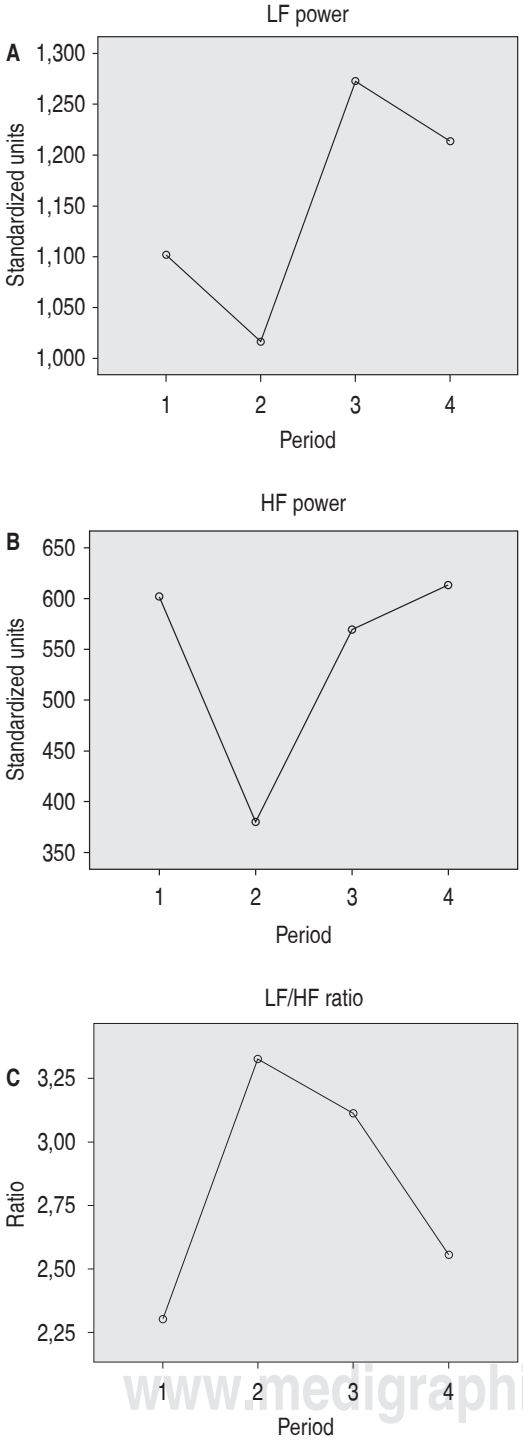

Figure 2: HRV evaluated through frequency-domain measures: LF, HF, and LF/HF ratio during the 48-hour period. Average HRV measured as **A)** LF, **B)** HF, and **C)** LF/HF ratio is shown for each of the four 12-hour periods.

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.

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Correspondence to:

Mauricio Duque-Ramírez
Tel: (+57 4) 444 7378
E-mail: mauricioduquemd@gmail.com

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Review

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Electrocardiographic abnormalities in subarachnoid hemorrhage

Anomalías electrocardiográficas en hemorragia subaracnoidea

José Miguel Gloria Escobar,* Juan Pablo Zuluaga García,* Laura Duque González,‡ Carlos Aníbal Restrepo Bravo§

Keywords: Electrocardiogram, subarachnoid hemorrhage, giant T wave, arrythmias, ventricular fibrillation, ventricular tachycardia.

Palabras clave: *Electrocardiograma, hemorragia subaracnoidea, onda T gigante, arritmias, fibrilación ventricular, taquicardia ventricular.*

ABSTRACT

Electrocardiogram abnormalities are particularly common among patients with subarachnoid hemorrhage (SAH). Phenomena such as ventricular tachycardia and fibrillation, torsade de pointes (mainly when a QTc is prolonged), sinus bradycardia, sinus tachycardia, atrial fibrillation, wandering atrial pacemaker, premature atrial, junctional, and ventricular complexes, atrioventricular block, neurogenic T waves, peaked P waves, shortened PR interval, inverted U waves and ST segment deviations have been described. Not only can these abnormalities mimic myocardial infarction or myocardial ischemia, but they also share an important prevalence with wall motion abnormalities like the Takotsubo cardiomyopathy. There have been few studies involving Holter monitoring in these patients, which constitutes an investigation subject with aims to standardize these complications in order to avoid adversely affecting discharge disposition and prolong in-hospital staying.

RESUMEN

Las anormalidades en el electrocardiograma son particularmente comunes en los pacientes con hemorragia subaracnoidea. Se han descrito fenómenos como la taquicardia y fibrilación ventriculares, taquicardia de puntas torcidas (principalmente cuando el intervalo QTc se encuentra prolongado), marcapaso atrial migratorio, complejos atriales, de la unión y ventriculares prematuros, bloqueo auriculoventricular, ondas T neurogénicas, ondas P picudas, acortamiento del intervalo PR, ondas U invertidas y desviaciones del segmento ST. Estas anormalidades no sólo pueden simular isquemia o infarto del miocardio, sino que también comparten una importante prevalencia con otras de la motilidad de la pared miocárdica, como la cardiomiopatía de Takotsubo. Pocos estudios han utilizado el monitoreo Holter en estos pacientes, lo que constituye un tema de investigación con miras a estandarizar este tipo de complicaciones para evitar afectar de forma adversa el alta de estos pacientes o prolongar su estancia hospitalaria.

INTRODUCTION

Subarachnoid hemorrhage (SAH) affects 30,000 people between the mid and late adulthood in the United States annually. It has a mortality rate of 30 to 45% and is more likely due to a congenital cranial base aneurysm rupture, followed by an aneurysm rupture of infectious or traumatic etiology and an arteriovenous malformation rupture.[1] Approximately 15-20% of patients with SAH do not have a vascular lesion on initial four-vessel cerebral angiography, and the causes of this phenomenon are diverse and often not identified.[2] Although SAH has a high mortality rate, it has been declining over time in western population; probably due to improvements in rate of smoking, hypertension, its clinical management, diagnostic accuracy and therapeutic measures.[3]

Apart from a clinical suspicion of a SAH based on a wide variety of signs including severe headache of abrupt onset, nausea, vomiting, nuchal rigidity and consciousness alteration, the electrocardiogram (ECG) can portray specific waveform morphology and rhythm alterations.[1] It has been evidenced in previous studies that SAH is associated with a variety of cardiac alterations, which include ventricular tachycardia and fibrillation (mainly when a QTc is prolonged), torsade de pointes,

* Medical student, School of Medicine.
‡ Cardiology Fellow.
§ Associate Professor, Medical Sciences, School of Medicine.

CES University. Antioquia, Colombia.

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sinus bradycardia, sinus tachycardia or atrial fibrillation, among others.[1]

Prevalence of ECG abnormalities in SAH patients

The prevalence of ECG abnormalities in SAH patients has been previously reported to range between 27 and 100%. This wide range of prevalence may be due to errors in study methods, number of patients or ECG readings. Because neurological patients do not routinely have ECG, underregistration is a common problem.[1] Another observation is that even though some might consider ECG recordings prior to the SAH not important, these should also be included to have an objective comparison in order to better risk-stratify patients, especially in the first hours following the hemorrhage. Brouwers et al found that the most pronounced ECG changes occurred during the first 72 hours after SAH,[4] while Di Pasquale et al found that 90% of patients had ECG abnormalities in the first 48 hours.[5] These results outline the importance of starting early ECG monitoring in these patients.

Pathophysiology

Crompton and Smith, suggested that the hemorrhage causes localized arteriolar vasospasm resulting in ischemic damage to the hypothalamus and its periphery.[6,7] This type of damage induces catecholamine release directly via the upper cervical sympathetic chain and indirectly via the pituitary-adrenal axis. Greenhoot et al, and Melville et al, demonstrated that direct electrical stimulation of the hypothalamus results in ECG abnormalities resembling those seen in SAH patients.[8,9] Rogers et al, reproduced constant changes in T waves by stimulating the right and left side of the hypothalamus and stellate ganglia respectively, which suggest a neurogenic response that ultimately is responsible for any particular changes in rhythm and myocardial wall.[10] Cruickshank et al, conducted a trial with 46 patients diagnosed with SAH by lumbar puncture recording a total of 197 ECGs and measured mean urinary catecholamines, mean urinary normetanephrine, mean urinary metanephrine and mean plasma cortisol. This trial demonstrated a statically significant correlation with high levels of plasma cortisol (100 μg/mL) with peaked P-waves ($n = 40$, plasma cortisol [PC] $= 27 \pm 10.8$, $p < 0.01$), peaked T-waves ($n = 21$, PC $= 27.3 \pm 7.8$, $p < 0.05$) and a PR interval lasting shorter than 0.13 msec ($n = 11$, PC $= 27.5 \pm 10$, $p < 0.01$), as well as high mean urinary catecholamine values in the abnormal ECG group in a period of 2 weeks.[11] Parekh et al found that patients with elevations in cardiac troponin I were more likely to have ECG abnormalities than patients without elevations in the biomarker.[12]

In general, factors that influence the development of ECG and ventricular function abnormalities include cerebral vasospasm (discussed above), hypoxia, electrolyte imbalance, and sudden increase in intracranial pressure triggering a sympathetic or vagal discharge due to compression or direct ischemic damage of brain structures,[1] particularly, the hypothalamus.

Morphological wave changes

These are primarily alterations in repolarization encompassing the T wave, U wave, ST segment and QTc interval. ST-segment elevation or depression and T wave inversion are frequently confused with myocardial infarction *(Figures 1 and 2)*.[1,13] In the most extensive study ever

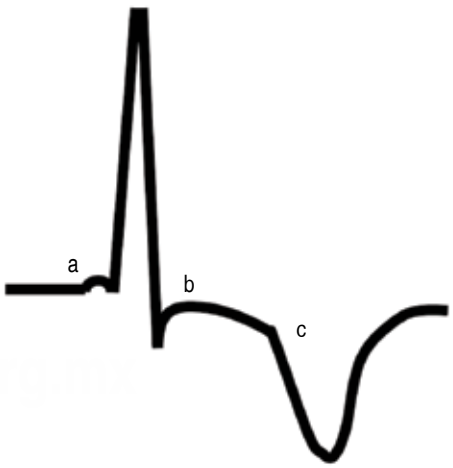

Figure 1: Schematic representation of the most common ECG findings on precordial leads (V3-V5): **a.** Short PR interval, **b.** ST segment depression, **c.** inverted and broad-based T wave.

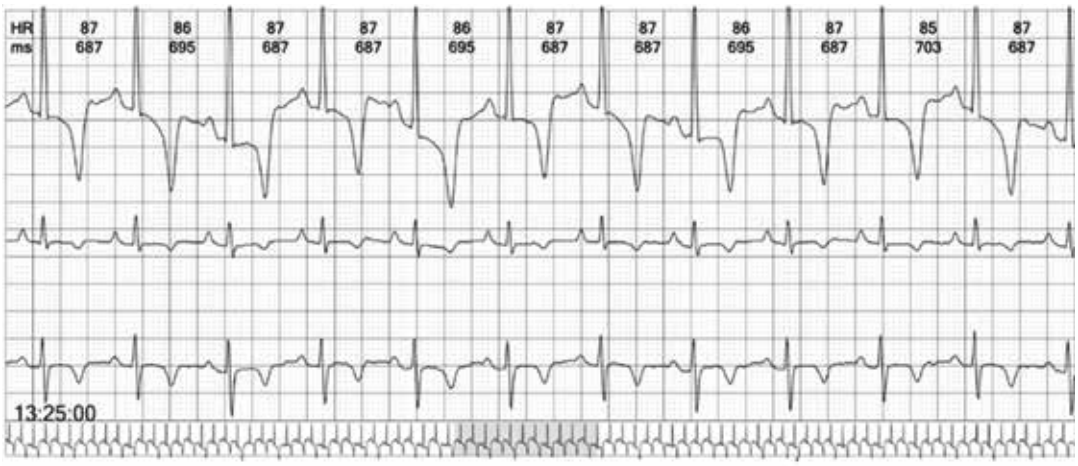

Figure 2: 24-hour Holter monitoring on a 64-year-old female with SAH. Recordings reveal characteristic inverted broad T waves and ST-segment depression. Taken with permission from CES Cardiology electrocardiographic database. Medellín, Colombia.

done on the matter, Rudehill et al[14] recruited 406 patients who were submitted to SAH preoperative ECG monitoring, and findings included high-amplitude R waves in 19% of subjects, ST depression in 15%, T-wave abnormalities in 32%, U waves greater than 1 mm in amplitude in 47%, and prolonged QTc interval (> 440 msec) in 23% of the patients. In a different study, Q wave alterations were found in 4 SAH patients after surgery and T wave alterations in 15 of them.[15] A prolonged QTc interval and abnormally large T waves were also noted. These «cerebral» or «neurogenic» T waves are characterized by slurring, and having a broad base; although they can be notched or even flat.[1]

In a relatively large study, a total of 61 patients for 12 days or until surgery occurred with a 12-lead ECG and cardiac monitoring for arrhythmias; of these patients, 26 had daily 12-lead ECG readings, and 43 of them had readings three times per week. The most common findings were prominent U waves, ischemic T waves, ST-segment elevation or depression, indicators of left ventricular hypertrophy, flat T waves and short PR interval.[4] Melin and Fogelholm found ECG changes in 86% of 14 subjects who died within seven days of SAH and in 73% of 62 subjects who survived more than 7 days.[16] A total of 26 patients died within the first 6 hours of SAH instauration (even before an ECG could be obtained). Common findings among the obtained ECGs were abnormal Q waves, ST-segment deviation, neurogenic T waves and QTc longer than 430 msec. In the one study that included Holter monitoring, a 12-lead ECG and cardiac monitoring from 120 patients with SAH, were obtained on the day of admission. Changes included ST-segment deviations in 37% of patients, prominent U waves in 16%, and T-wave abnormalities in 12%. Also, 42% of patients had a prolonged QTc interval. Transitory ST-segment depression greater than 1.5 mm lasting 10 to 30 minutes was detected in 7 patients. ST-segment elevation lasting 20 minutes occurred in 1 patient during cerebral angiography along with bigeminal premature ventricular complexes. Abnormalities involving atrial depolarization including notably peaked P waves (> 2.5 mm in amplitude) and short PR intervals (< 100 msec), were also observed.[5]

ARRHYTHMIAS

Despite flaws in accurately monitoring for arrhythmias in previous studies, several alterations have been reported, such as sinus bradycardia, sinus tachycardia, wandering atrial pacemaker, atrial fibrillation, premature atrial, junctional, and ventricular complexes *(Figure 3)*; atrioventricular block, torsade de pointes and ventricular tachycardia.[1]

In his study, Di Pasquale et al, obtained a total of 107 correct Holter readings, and cardiac arrhythmias were detected in 96 (90%) of the 107 patients, premature ventricular complexes, including multiform premature ventricular complexes, couplets or triplets, and the R-on-T phenomenon, were detected in 49 patients (46%) and five of the patients with frequent premature ventricular complexes also had non-sustained ventricular tachycardia (defined as 3 or more consecutive premature ventricular complexes, torsade de pointes occurred in 4 patients and progressed to ventricular fibrillation and asystole in 1 of the 4.[5]

Holter monitoring was repeated 48 hours later in all patients who had malignant alterations, but no further arrhythmias occurred. Of the 107 patients, 39 (36%) had supraventricular arrhythmias, including premature supraventricular complexes, non-sustained supraventricular tachycardia, and atrial fibrillation.[1] Thirty-two patients (30%) had sinus tachycardia (heart rate > 120/min), 32 (30%) sinus arrhythmia, 42 (39%) sinus bradycardia (heart rate < 50/min), and 23 (21%) sinoatrial blocks. Other rhythm disturbances, such as wandering pacemaker, sinus arrest greater than 3 seconds, 2:1 atrioventricular block, atrioventricular dissociation, and idioventricular rhythm were also found.[1] Di Pasquale et al, found that both severity and frequency of arrhythmias were more significant in the 62 patients studied within 48 hours of SAH onset and that patients with malignant ventricular arrhythmias had a much more prolonged QTc interval (590 ± 52 msec) and serum levels of potassium less than 3.5 mmol/L.[5]

WALL MOTION ABNORMALITIES

Abnormalities in the myocardial wall movement can certainly confuse the attending physician when it comes to reading an ECG; especially given the fact that they can sometimes suggest other pathological entities such as myocardial ischemia or acute myocardial infarction.[17] Although these changes have been reported to be benign in most cases, there is a significant prevalence of other very similar pathologies associated with SAH that can threaten the patient´s life and most always be taken in consideration and differentiated.[18-20] For instance, the type of resemblance that these abnormalities have with myocardial infraction in ECG recordings can not only generate delay and confusion at the time of diagnosis, but also

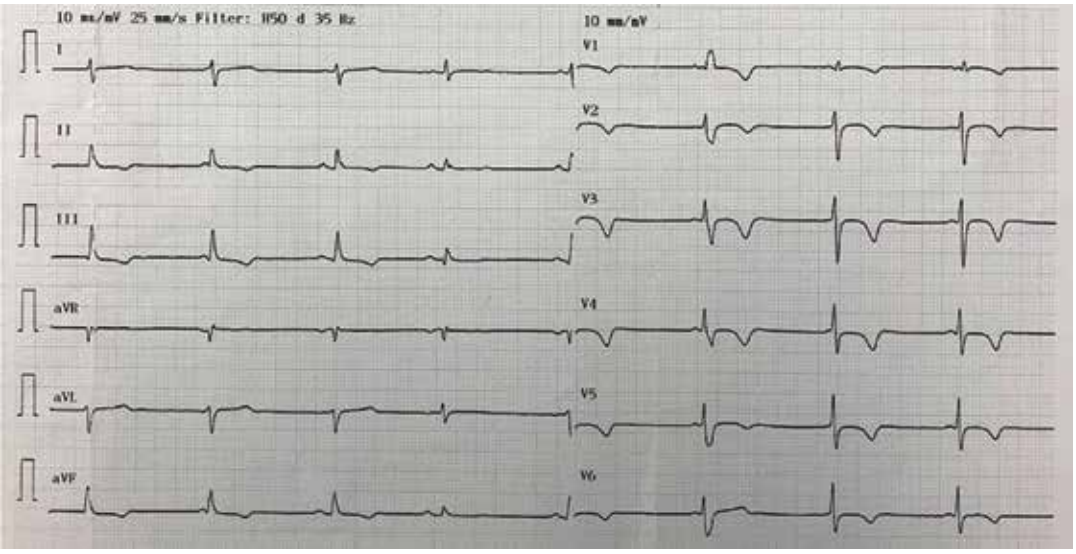

Figure 3: Twelve lead ECG in a 53-year-old man admitted to the intensive care unit due to SAH, exposing complete AV block with escape junctional rhythm, T wave inversion in precordial leads and 2 ventricular premature complexes. Taken with permission from CES Cardiology electrocardiographic database. Medellín, Colombia.

Table 1: Most common wave electrocardiographical and ventricular function abnormalities found by each author.

Summary of findings		
Morphological wave changes		
Brouwers et al[4] Cropp and Manning et al[15]	PR interval Q wave	Short > 1 mm
Melin and Fogelholm et al[16] Brouwers et al[4] Rudehill et al[14] Di Pasquale et al[5]	T wave	Inverted Broad base Notched Flat
Rudehill et al[14]	R wave	High amplitude
Brouwers et al[4] Rudehill et al[14] Di Pasquale et al[5]	U wave	Prominent (> 0.1 mv)
Melin and Fogelholm et al[16] Brouwers et al[4] Rudehill et al[14] Di Pasquale et al[5]	ST segment	Elevation Depression (more common)
Melin and Fogelholm et al[16] Rudehill et al[14] Di Pasquale et al[5]	QTc interval	Prolonged
Arrythmias		
Di Pasquale et al[5]	Supra-ventricular	Sinus bradycardia Sinus tachycardia Wandering atrial pacemaker Atrial fibrillation
	Ventricular	Ventricular tachycardia Torsade de pointes
	Premature complexes	Atrial Junctional Ventricular
	Blocks	Sinoatrial Atrioventricular
Ventricular function abnormalities		
Van der Bilt et al[25] Kadooka et al[38]	Takotsubo cardiomyopathy	ST elevation / depression T wave inversion QTc interval prolongation

create possible incorrect therapeutic actions that can aggravate the patient's condition such as antiplatelet, anticoagulant and fibrinolytic therapy.[21]

Taking into account that the alterations found in the ECG are not the only regarding cardiac perfusion per se, there has been evidence of dysfunction in the heart wall motion as well,[22-24] specially Takotsubo cardiomyopathy (TCM).[25-27] Van der Bilt et al conducted a prospective, multicenter, cohort study involving 277 patients with aneurysmal SAH; 58 of which (21%) developed wall motion abnormalities, and also reported that 25 of the 57 abnormalities (9%) consisted of hypercontractility of apical segments, compatible with TCM.[25]

TCM was first described in 1991 by Sato et al, as a clinical entity caused by a high level of psychosomatic stress.[28] This syndrome consists of a global dysfunction of the left ventricle which in turn causes transient hypokinesis, akinesis or dyskinesis of the apex and midventricle with hyperkinesis of the basal left ventricle segments.[29,30] The electrocardiographic presentation of TCM resembles an acute myocardial infarction, portraying elevation of the ST-segment, T-wave inversion and prolonged QTc interval.[27,28] Multiple studies have shown the association between SAH and TCM, showing predominance female phenotype (76%), especially postmenopausal women, and the mean age upon presentation was 60 ± 8 years,[30-32] with a prevalence of 4-15%,[31,33-35] a mortality rate of < 2% and a recurrence rate between 5 and 11% in this population.[32,36,37] Kadooka and collaborators presented a study with 450 patients with diagnosis of aneurysmal SAH. Ten of these patients developed TCM along with inverted of flattened T waves (100%), QTc prolongation (< 0.45 msg; 90%), ST-segment elevation (60%) and ST-segment depression (20%). In addition, the study found that the recovery of the wall motion varied between 1 to 2 weeks, as opposed to the improvement of abnormalities on ECG that had an average of 3-4 weeks in most of the patients.[38] The importance of the period between the normalization of wall motion and the abnormalities in ECG lies on the risk of developing arrhythmias like non-sustained ventricular tachycardia, paroxysmal atrial fibrillation and ventricular fibrillation.[1,38-40]

In *Table 1*, all findings described by the authors mentioned in this review are included to give a better comprehensive view of all cardiac ECG and ventricular function alterations reported in patients with SAH.

CONCLUSIONS

ECG abnormalities associated with aneurysmal SAH have been proved to affect discharge disposition and prolonged hospital stay,[41] and because few studies have effectively involved Holter monitoring in these patients, this constitutes a matter of investigations with aims to standardize this extremely wide range of electrical cardiac complications in this central nervous system pathology.

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Correspondence to:

José Miguel Gloria Escobar
Tel: (+57) 31 8844 3823
E-mail: josemiguelgloria@gmail.com

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Review

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Hands-only cardiopulmonary resuscitation and public access defibrillation, the need for cardio-protected areas implementation in Mexico

RCP sólo con las manos y DEA de acceso público, la necesidad de implementar áreas cardio-protegidas en México

Humberto Rodríguez-Reyes,* Mayela Muñoz-Gutiérrez,‡ Enrique Asensio-Lafuente§

Keywords: Cardiopulmonary resuscitation, automated external defibrillator, sudden cardiac arrest, sudden death.

Palabras clave: *Reanimación cardiopulmonar, desfibrilador externo automático, paro cardiaco súbito, muerte súbita.*

ABSTRACT

Sudden cardiac arrest (SCA) is one of the main worldwide health problems. It is estimated that it is responsible for 30% of cardiovascular deaths and up to 20% of total adult mortality. The chance of survival for a SCA victim is related to the timely interventions after the event in the first 5 minutes there is a greater chance of survival of the victims. Hands-only cardiopulmonary resuscitation (CPR) and public access automated external defibrillator (AED) use, are so far the best strategy to increase the victim's survival in an out-of-hospital setting. In this work, the meaningful role of hands-only CPR and public access AED to increase the SCA victim's survival in the community are reviewed, as well as the importance of implementing cardio-protected areas in Mexico.

RESUMEN

El paro cardiaco súbito (PCS) es uno de los mayores problemas de salud a nivel mundial. Se estima que es responsable de 30% de mortalidad cardiovascular y de 20% de la mortalidad total en los adultos. La posibilidad de recuperación para una víctima de PCS depende del tiempo en que se inicie la atención posterior a ocurrido el evento, en los primeros cinco minutos se tiene mayor posibilidad de supervivencia de las víctimas. La reanimación cardiopulmonar (RCP) sólo con las manos y el uso de desfibrilador externo automático (DEA) de acceso público son la mejor estrategia para lograr proporcionar atención temprana y mejorar la supervivencia de las víctimas de un PCS dentro y fuera de un hospital. En el presente artículo se revisa la importancia de la RCP sólo con las manos y del uso de DEA de acceso público para mejorar la supervivencia de las víctimas de PCS en la comunidad, así como la importancia de implementar áreas cardio-protegidas en México.

* Cardiology, Electrophysiology and Internal Medicine, FACC, FHRS, AHA Instructor of BLS (basic life support) and ACLS (advances cardiovascular life support), AHA, LHRS, ESC member. Coordinador del capítulo de paro cardiaco, muerte súbita y reanimación cardiopulmonar de la Asociación Nacional de Cardiólogos de México (ANCAM). Sociedad Cardiovascular y Arritmias (SOCAyA). Aguascalientes, México. ORCID: 0000-0003-3164-8515.

INTRODUCTION

Sudden cardiac arrest (SCA) is one of the main worldwide health problems. It is estimated that there are almost 5.3 million cases every year,[1] thus being responsible for 30% of the cardiovascular deaths and 20% of the total global adult mortality.[2] Most of SCA patients end-up as sudden death (SD) victims, and this outcome is frequently among subjects that do not benefit from early CPR and AED.[3] Currrently, more patients show non-shockable rhythms such as asystole or pulseles electric activity (PEA) as the cause of SCA at home, where almost 80% of the community cardiac arrests occur.[4] Nonetheless, SCA might also be related to a shockable rhythm as ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) that are regularly encountered in the out-of-home place setting or related to sports activities. This represents nearly 20% of the community's SCA events among children and adults.[5,6] At the present time, the chance of survival for SCA victims is less than 10%,[7,8] but this can be significantly improved among victims with a shockable rhythm (VF, pVT) that are early treated with CPR and AED.[8,9]

‡ Cardiology and Cardiac Rehabilitation. Sociedad Cardiovascular y Arritmias (SOCAyA). Aguascalientes, México.
§ Cardiology and Electrophysiology, FHRS. Hospital H+ Querétaro, México.

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Hands-only CPR and «chain of survival» in the community

It has been demonstrated that hands-only CPR in the community is as effective as CPR with compressions and ventilation support,[10] thus making it the preferred method among lay-persons.[11,12] Usually, the out-of-hospital care sequence for SCA is initiated with the early detection of the victim, emergency medical services activation (call 911 in Mexico), asking for an AED and start CPR, with particular emphasis on chest compressions and use of the AED as soon as it is available *(Table 1)*. When a SCA victim with a shockable rhythm is treated within the first two minutes after the cardiac arrest, the survival rates might go as high as 71% with an adequate neurological recovery.[13] In Mexico, several efforts have been made in different communities to improve SCA survival. For example, in the city of Querétaro, several massive CPR public training sessions have been organized since 2008 to date. The survival rate of patients went from 0% to an initial marginal improvement in survival.[14,15]

Public access AED

In large populations, the Hands-only CPR and early defibrillation (AED) training programs have shown to be effective because they encourage the community's implication in early CPR and AED administration and reduce mortality rates.[16] This is particularly evident among SCA victims with shockable rhythms in sports centers or units that have readily available AED's and public CPR training.[17] In order to protect more population, strategic places are chosen to locate public AED's, and the devices are also included in different emergency vehicles so the SCA victims can be treated sooner.[18] A local analysis showed that first responder units (police cars, for example) equipped with AED could lower the financial costs per life saved from 5.8 million pesos to 0.5 million pesos when compared with advanced life support ambulances. This is a way to optimize the resources and personnel use.[19] Some countries have reported that by-stander CPR and AED use prior to the emergency medical services arrival has increased and that there is a higher community participation in resuscitation maneuvers, thus reducing mortality, increasing survival rates and improving the neurologic outcomes of the SCA victims. Those results emphasize the training programs meaningfulness and are a stimulus to continue training and promoting community based-CPR and AED use.[13,20]

Table 1: SCA victim attention in the community, Hands-only CPR and public access AED.

1. Acknowledge the SCA victim (sudden collapse, non-responsive, does not move, does not breathe, is pale or cyanotic)
2. Call the local Emergency Medical Services number (Mexico 911), ask for an AED and put the call on speaker to receive assistance from the dispatcher
3. Initiate chest compressions in the center of the chest, between both nipples, at a 100 to 120 compressions per minute rate, with 5 to 6 cm depth, or 4-5 cm in children until an AED is available or EMS assistance arrives
4. Fast use of the AED
   A. Open and follow the instructions in the AED
   B. Place the chest patches as indicated, remember to use pediatric patches in children less than 8 years-old. Do not touch the victim while the AED analyzes the rhythm
   C. If a shock is required, the AED will indicate it
   D. Remember to say «stand back» and assure that no one touches the victim before applying the shock
   E. Push the blinking button to administer a shock
5. Re-start chest compressions until the patient regains consciousness, EMS assistance arrives or until the AED indicates it

SCA = Sudden Cardiac Arrest; CPR = Cardiopulmonar Resuscitation; AED = Automatic External Defibrillator; EMS = Emergency Medical System.

Table 2: Prehospital interventions and survival in the city of Querétaro of victims of out-of-hospital cardiac arrest, registered with the Utstein-Style methodology.[15,19]

	* ↓ 2006	* 1 ↓ 2009	2013	* ↓ 2017	2018	* ↓ 2019
n	147	204	79	62	68	68
CPR prior to EMS arrival (%)	2.0	10.8	44.4	NA	NA	NA
CPR by police (%)	NA	NA	1.5	24.5	18.4	24.2
Defibrillation by police (%)	NA	NA	NA	2.0	0	1.6
Patients with shockable rhythms (%)	NA	9.6	1.5	0	7.7	10.0
ROSC (%)	30.0	1.85	20.3	24.0	42.3	29.8
Survival (%)	0	0	2.5	6.45	4.4	1.47

* Change of the municipal goverment. 1. Medical Emergencies Regulator Center Start of operations (2011). 2. Querétero «Cardioprotected» City.
CPR = Cardio-Pulmonary Resuscitation; EMS = Emergency Medical Services; ROSC = Return Of Spontaneous Circulation; NA = non available.

Hands-only CPR and AED use Program in Mexico

Some Mexican States have already implemented «cardio-protected» areas with community hands-only CPR training and public access defibrillation, but the programs have not been implemented nation-wide yet. This is why it is important to promote the cardio-protected areas implementation in schools, large buildings, hotels, business centers, bus terminals, airports, malls, retirement facilities, residential clusters, sports centers, gyms, emergency medical units, medical offices units and so on. Any place with a potential to gather more than 500 people at a time, should ideally be a cardio-protected area. In this regard, it could also be useful to have every emergency services vehicle equipped with an AED. We believe that the best way to achieve cardio-protection in our country is to implement generalized Hands-only CPR training and to place AED's in public places in a pattern similar to the present fire extinguisher placement legislation. This is a way to stimulate the public and private authorities participation, considering that they are the mainstay for the complete population's protection. In Mexico we do not have comprehensive statistics on the incidence of SD. According to a preliminary study with a low number of interventions, in Querétaro, the one-year survival rate after implementation of CPR training for the public (while obtaining their driver's license and through repeated training in public events) and police officers, and after equipping some police cars with AED, has raised from 0% to 6.4% in a ten year-period *(Table 2)*.[15,19] Nonetheless, it is important to establish a public health policy that ensures the continuity of the training efforts in order to maintain and increase the survival rate of these patients. A nation-wide permanent implementation of the hands-only CPR and public access defibrillation programs could promote several health improvements such as: 1) Increase the awareness and understanding of the general population and healthcare personal about this important problem, 2) Favor more preventive behaviors in the population in order to avoid a SCA, 3) Reduce the incidence of SCA and SD, and 4) Improve the survival rate of SCA victims in the community.

CONCLUSIONS

SCA remains a main public health concern worldwide. Early Hands-only CPR and public access defibrillation performed by lay-persons

might significantly increase the victim's survival, especially among victims with a shockable rhythm. Nonetheless, those early interventions require large community based Hands-only CPR programs and enough AEDs available in public areas with certain features, mainly, any place that can gather 500 people or more at the same time. To achieve full coverage of the population, it is necessary the implementation of AEDs be a requirement as is the current normativity about the use of fire extinguisher in our country, which would allow the participation of all sectors (public and private), and we could achieve improvements in several important aspects of health in our population.

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Correspondence to:

Dr. Humberto Rodríguez Reyes FACC, FHRS, AHA, LAHRS, ESC, SEC member
Coordinador del capítulo de PCS, MS y RCP del ANCAM 2019-2020
Presidente Sociedad Cardiovascular y Arritmias (SOCAyA).
E-mail: humbertorodriguezr@hotmail.com

Cardiovascular and Metabolic Science

Statistics corner

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Clinical versus statistical significance

Significado clínico versus estadístico

José Luis Moragrega Adame*

Statistical significance refers to the likelihood that a relationship between two or more variables, is caused by something other than chance.[1] Statistical hypothesis testing is used to determine whether the result of a data set is statistically significant. In medicine usually it is used for the comparison of some characteristics of two groups. Two examples are patient's age or weight previous to the intervention or glucose levels with the administration of two different drugs. Since in medicine we always work with samples and never with a whole population, we make inferences from the sample to estimate with the statistics the parameter whose values we really do not know *(Figure 1)*. Then we use the knowledge derived from taking many samples from a population, distributing them (central limit theorem and the standard error of the mean), knowing the properties of the distribution (e.g. normal or Gaussian curve) and finally calculating the probability that the sample means difference is due to chance or shows a true difference present in the universe (p value). There is a risk to be wrong if we accept the difference as being true when in fact it does not exist (type I or alfa), and also a risk to accept the null hypothesis of no difference when in fact it does exist (type II or beta) *(Figure 2)*.

All the preceding discussion is related to the mathematical probabilities of the sample reflecting the universe appropriately, but clinical importance is a completely different matter.[2] If the investigation is accepted in its

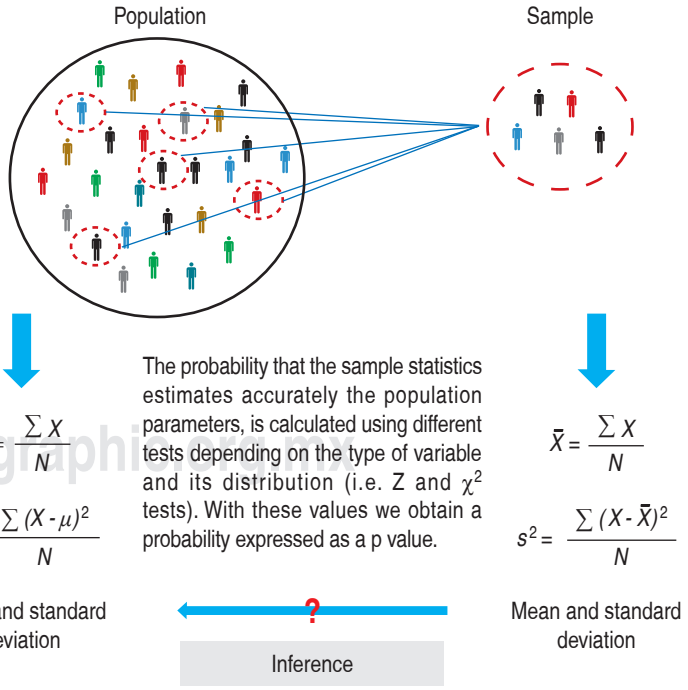

Figure 1: Sampling of a population, formulas to calculate mean and dispersion. The results obtained in the sample are used to estimate the probability that they reflect the population parameter values.

* Hospital Torre Médica. Medicina privada. Irapuato, Guanajuato, México.

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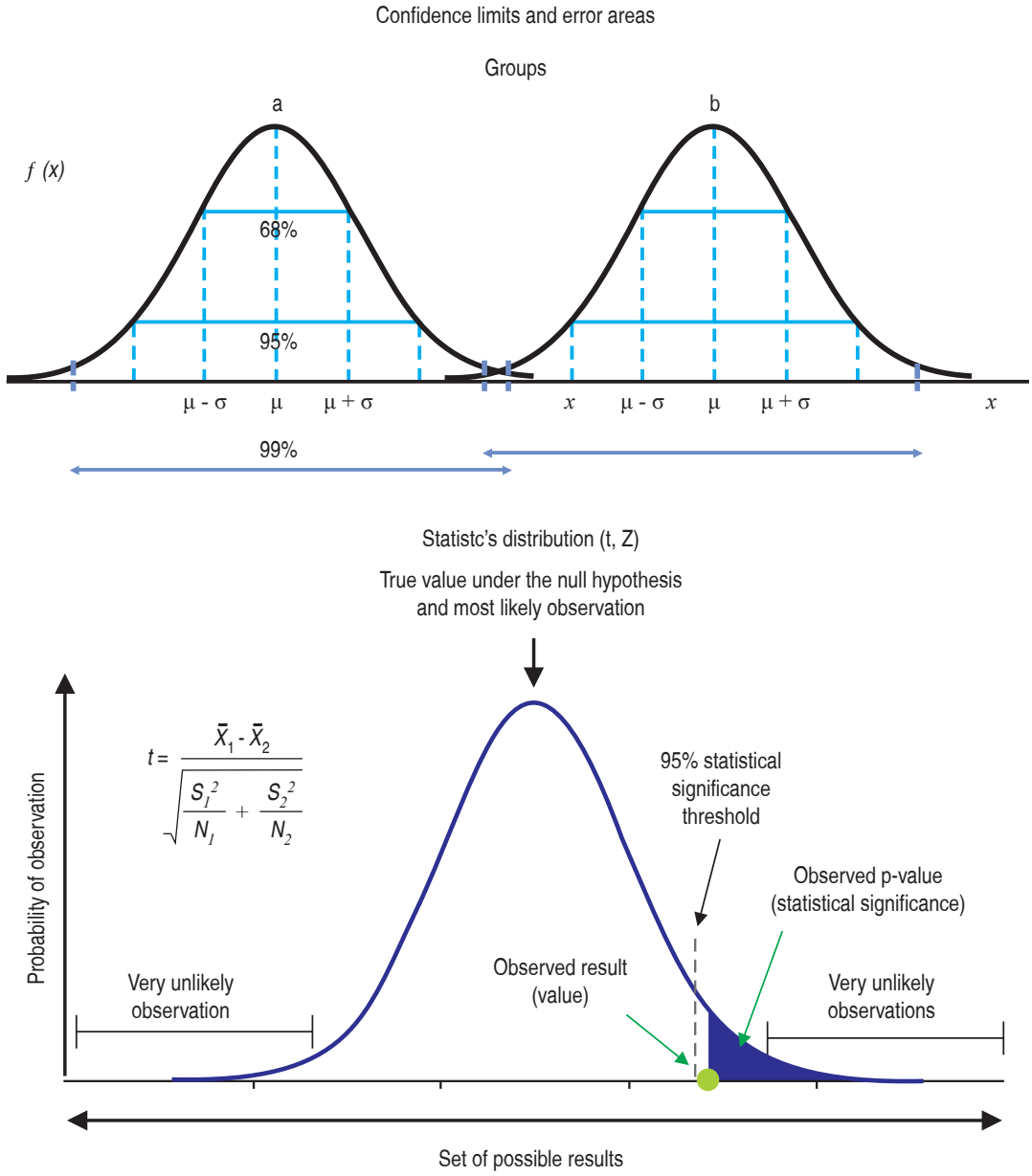

Figure 2:

On the left side, distribution curves that point to the central trend (mean) and dispersion as standard deviation for two groups. In the right curve distributions of statistics (z or **t**) with the respective formula and limits to reject the null hypothesis (95% confidence). https://www.simplypsychology.org/p-

design, execution and conclusions as having internal validity, the extrapolation to different populations has to be done with extreme care (external validity). The magnitude of the effect is to be analyzed looking at the differences of attributable risk and not in relative risk. The GRADE scale or other methods of qualifying a paper is a first step in deciding if the concept is solid. The clinically important difference can be calculated following the recommendations of groups like «The clinimetrics corner».

NNT or number needed to treat shows that the larger the effect, the smaller the NNT to obtain a benefit (e.g. avoiding a death). Consult The NNT page and the publications of David Sackett.

For example, we can observe a difference of 1% in absolute risk reduction (stroke or death) in five years of treatment (4% in the control group and 3% in the intervention group) but express it as a relative reduction of 25% because 1% is ¼ of the control group risk. The

NNT would be treating 100 patients for 5 years to reduce a case. As the study includes 5000 patients, the difference is statistically significant.

But does it have a clinical importance? To decide in favor of an intervention it has to be proven in its efficacy, then in its effectiveness and finally in its cost-effectiveness as shown in the Cochrane model. Concepts to be considered include if the hypothesis has been subjected to falsification or confirmation in different settings, and the acceptance by patients and the medical community.

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Correspondence to:

José Luis Moragrega Adame MD, FACC
Hospital Torre Médica
Irapuato Gto.
E-mail: jlmoragrega44@yahoo.com.mx

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Abnormal origin of the right pulmonary artery from the aorta. Case report and literature review

Nacimiento anómalo de la rama pulmonar derecha de la aorta. Reporte de caso y revisión de la literatura

Oscar Rene González-Hernández,* Roberto Cano-Zárate,‡ Christian González-Padilla,§ Tomás Miranda-Aquino,‖ Michel Machuca-Hernández‖

Keywords:
Abnormal origin, right pulmonary branch, aorta, corrective surgery.

Palabras clave:
Nacimiento anómalo, rama pulmonar derecha, aorta, cirugía correctiva.

ABSTRACT

A 43 y/o male with a history of patent ductus arteriosus and corrective surgery of the defect performed at 11 years of age. He remained asymptomatic for a long time until he developed shortness of breath on moderate effort, associated with palpitations, productive cough and hemoptysis. On the initial investigation by Internal Medicine, he was diagnosed with a right basal pneumonia, and as part of the diagnostic approach, a chest CT scan was made, which reported an abnormal origin of the right main pulmonary artery from the ascending aorta. He was transferred to the National Institute of Cardiology, where a MRI and a cardiac angiography were performed. The diagnosis was confirmed and pulmonary hypertension was also reported. The case was discussed by the heart team, and it was decided to take him to corrective surgery. The procedure was performed two months later, with the implantation of the right pulmonary branch to the main pulmonary artery using a synthetic Dacron tube. This case is presented, since it is extremely rare to find such a pathology, making the diagnosis in adulthood, with an insidious clinical presentation, which also has an adequate clinical evolution, after surgical repair.

RESUMEN

Paciente masculino de 43 años, en el cual se detecta persistencia del conducto arterioso a los 11 años de edad, por lo cual se realiza cirugía correctiva a dicha edad. Se mantiene asintomático por largo tiempo hasta que inicia con disnea de moderados esfuerzos, acompañado de palpitaciones, tos productiva y hemoptisis. Es abordado en un principio por Medicina Interna, quien realiza el diagnóstico de Neumonía basal derecha; además, como parte del abordaje, se realiza tomografía axial computada de tórax, en la cual se encuentra el hallazgo de origen anómalo de la rama derecha de la arteria pulmonar, con procedencia de la aorta ascendente. Es trasladado al Instituto Nacional de Cardiología, donde se realizan estudios complementarios como resonancia magnética y cateterismo cardiaco derecho e izquierdo, corroborando dicho diagnóstico y determinando la presencia de hipertensión pulmonar. En sesión médico-quirúrgica, se decide hacer cirugía de corrección, la cual se lleva a cabo casi dos meses después, con reimplante de la rama anómala a la arteria pulmonar y ayuda de la colocación de un tubo de Dacrón. Posterior a la cirugía, el paciente presenta adecuada evolución clínica.

* Cardiologist. Department of Cardiology. Hospital Civil de Guadalajara «Fray Antonio Alcalde». Guadalajara, Jal.
‡ Department of Cardiac Magnetic Resonance. National Institute of Cardiology «Ignacio Chávez». Ciudad de México.
§ Chief of Cardiology Division. Department of Cardiology. Hospital Civil de Guadalajara «Fray Antonio Alcalde». Guadalajara, Jal.
‖ Cardiology Resident. Department of Cardiology. Hospital Civil de Guadalajara «Fray Antonio Alcalde». Guadalajara, Jal.

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INTRODUCTION

Hemitruncus, is a rare condition that represents the 0.05% of congenital heart anomalies.[1] One of the lungs is irrigated by the aorta, whereas the other is perfused by the main pulmonary artery, in the presence of two semilunar valves.[2]

This condition was first described by O. Fraentzel, in 1868. The anomalous origin of the right pulmonary artery from the aorta is 5-8 times more common than the anomaly of the left pulmonary artery. In 20% of the cases it is reported as an isolated malformation.[2] We present the case of this interesting pathology in an adult patient, in whom it was not possible to achieve a precise diagnosis at an early age, operated at 11 years of age for the closure of a patent ductus arteriosus.

CLINICAL CASE

A 43 y/o male patient, who was born and actually is resident in Mexico City. His past

medical history was only positive for the exposure to *Trypanosoma cruzi* in his childhood and a blood transfusion when he was 11 y/o during the surgical closure of a patent ductus arteriosus at the National Institute of Cardiology. He denies consumption of alcohol, tobacco or drugs, and has no history of chronic diseases.

The patient started his present illness complaining of shortness of breath on moderate efforts, along with palpitations, productive cough and hemoptysis. He was hospitalized in the Internal Medicine Department, where they found signs that were compatible with a right lower lobe pneumonia. A chest CT scan was made, reporting cylindrical bronchiectasis and as an incidental finding the abnormal origin of the right pulmonary artery from the ascending aorta. According to the abovementioned, it was decided to continue the investigation and treatment at the National institute of Cardiology.

On physical examination, he showed no signs of heart failure. The apex was palpated at the 5th intercostal space of the left mid-clavicular line, with a 2 cm diameter apical impulse. He also had a left lower parasternal heave. On auscultation he had a normal S1, with physiological splitting of the S2 on inspiration and an increased intensity of the pulmonary component of the second heart sound; drawing the attention the presence of a holosystolic murmur at the tricuspid valve area, with a III/VI intensity. All these signs pointing to an incipient pulmonary hypertension diagnosis.

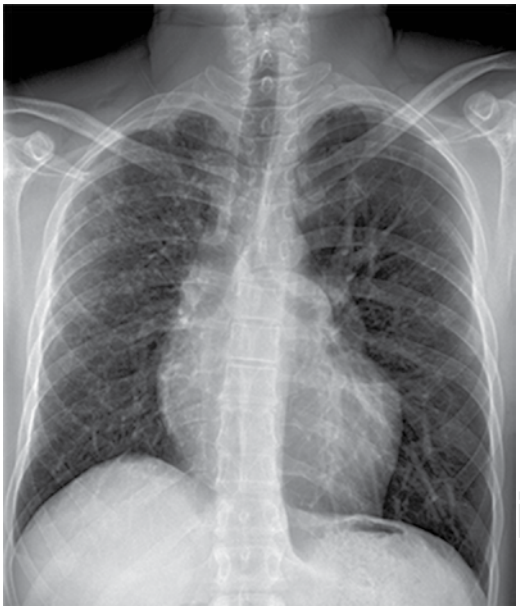

Figure 1: PA view chest X-ray, showing mild upper zone vascular flow redistribution with right lung predominance, along with enlarged pulmonary arteries with right predominance as well.

The PA (posteroanterior) view chest X-ray showed mild pulmonary flow redistribution, with a right lung predominance, along with a prominent right pulmonary artery *(Figure 1)*. A 12-lead electrocardiogram (ECG) showed an incomplete right bundle branch block and left ventricular diastolic overload *(Figure 2)*.

As part of the diagnostic approach, a transthoracic echocardiogram was performed, reporting non-dilated cardiac chambers, normal left ventricular diastolic function, a normal systolic function of both ventricles and normal valve function; it was described that the right pulmonary artery emerged from the ascending aorta.

Afterwards, to detail the vascular anatomy, a cardiac MRI was made, in which it was confirmed the anomalous origin of the right pulmonary artery from the ascending aorta as well as the following data: mild dilation of the right atrium, normal left ventricular systolic function with a left ventricular ejection fraction (LVEF) of 56%, right ventricular diameter in the upper normal limit, with a mild systolic dysfunction: ejection fraction of 45%, and with the presence of a mild tricuspid insufficiency *(Figures 3A and 3B)*.

In the inversion-recovery sequence, after the IV contrast material administration, it was observed a non-ischemic delayed enhancement pattern *(Figures 4A and 4B)*. HASTE sequence showed hyperintense areas at the apical lobe of the right lung; and as the most relevant finding, it is described that the right pulmonary artery emerges from the posteromedial side of the ascending aorta, with a diameter of 20 mm *(Figures 3C and 3D)*.

Considering the possibility of a surgical correction and specifically, to evaluate the presence of pulmonary arterial hypertension, a coronary and pulmonary angiographies were performed *(Figure 5)*, reporting the following findings:

- Normal coronary arteries.
- Oxymetric jump was not detected.
- Right pulmonary artery (RPA): vasculature with heterogeneous filling, tortuous vessels, with decrease in monopedial vessels and slow washing.
- Left pulmonary artery (LPA): vasculature with homogeneous filling and adequate amount of monopedial arteries.
- A 100% oxygen challenge was performed that showed no change in recorded pressures.

In the following table, we show the different pressure recordings in the evaluated cardiac chambers *(Table 1)*:

According to the cardiac catheterization results, it was concluded that there were signs of irreversible pulmonary arterial hypertension.

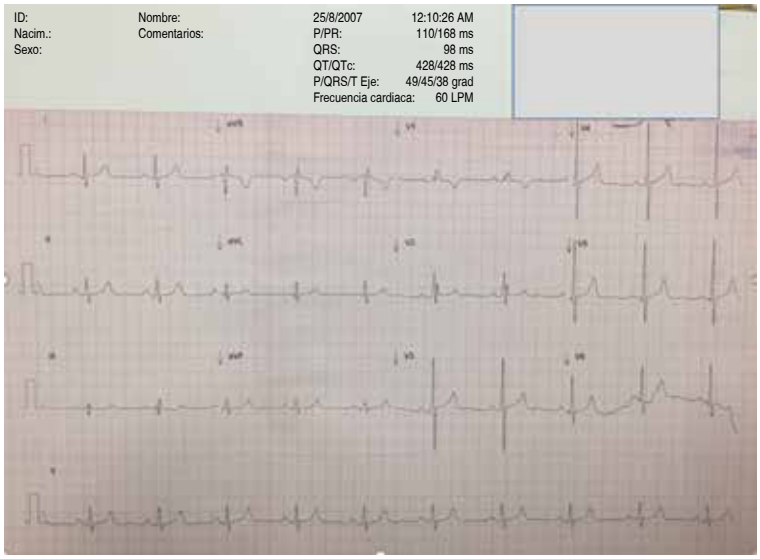

Figure 2: Twelve lead ECG, showing normal sinus rhythm, incomplete right bundle branch block and left ventricular diastolic overload.

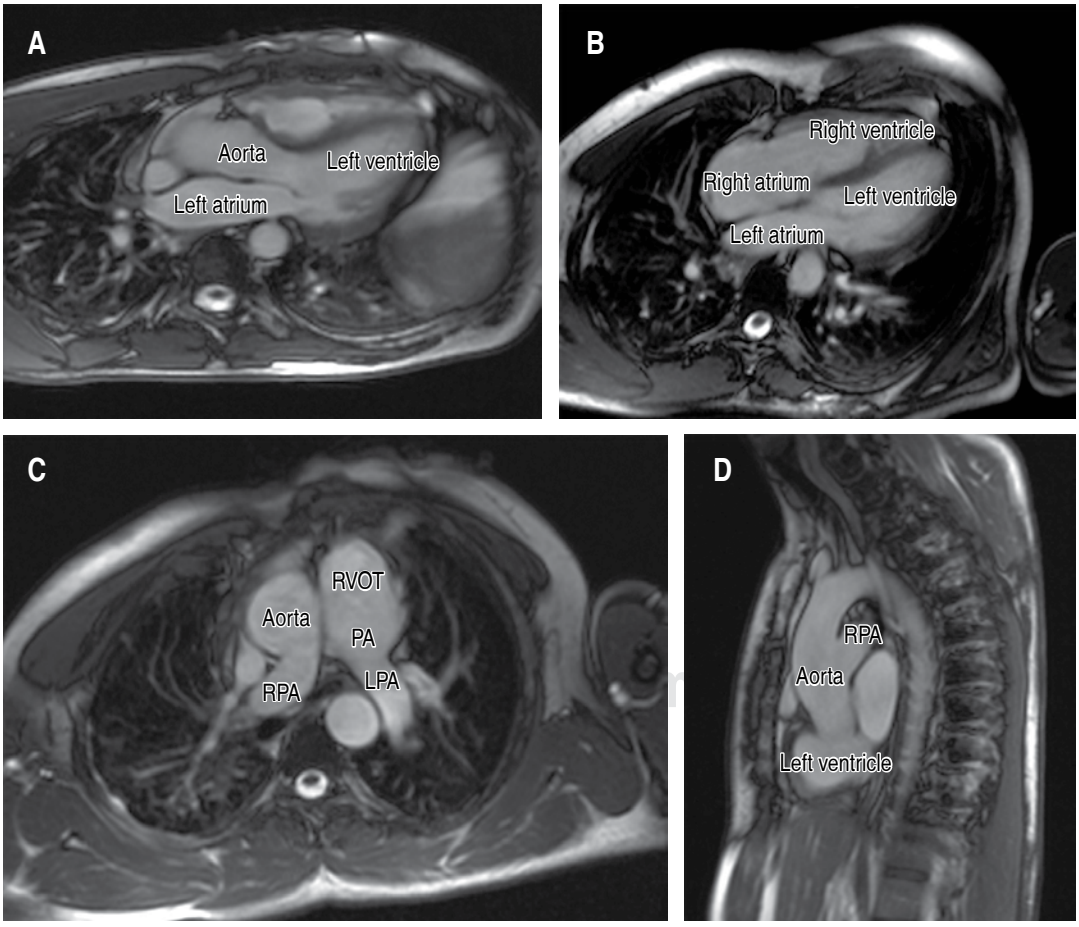

Figure 3:

Cardiac magnetic resonance (CMR) echo (Fixed) 3-chamber **(A)** and 4-chamber view **(B)**, showing normal cardiac diameters. CMR cine echo-gradient (fixed) axial **(C)** and sagittal plane **(D)**, demonstrating the origin of the right pulmonary artery from the aorta. LPA = left pulmonary artery, PA = pulmonary artery, RPA = right pulmonary artery, RVOT = right ventricle outflow tract.

However, in this particular case, the pulmonary artery pressure recording is unreliable due to the fact that the right pulmonary artery pressure is affected by its direct connection with the aorta and systemic blood pressure, that can finally impact in the pulmonary circulation.

In the background of a relatively young patient, with no other comorbidities, on a class I functional capacity of the New York Heart Association (NYHA) classification, in addition to undilated right and left ventricles, preserved right systolic function and LVEF, it was decided to take this patient to surgery.

In this particular case, the right pulmonary artery was redirected to the main pulmonary trunk, using a 16 mm woven Dacron tube and an 8 mm atrial septal defect was created as well. All these under extracorporeal circulation assistance. The patient was discharged without complications.

Two months after surgery, a chest CT scan was performed, showing post-operative modifications in the right pulmonary artery, as well as the graft patency, without evidence of stenosis or leakage. In order to evaluate the pulmonary vasculature hemodynamic evolution, a follow-up pulmonary angiogram was done. It was reported a remarkable pulmonary arterial pressure reduction, as well as a fall in pulmonary vascular resistance with 100% oxygen administration. Another oximetry run was taken but no step up was detected. The pulmonary arterial pressure recording after oxygen administration was 68/19 mean 41 mmHg and the pulmonary vascular resistance was 489 dynes, representing less than 2/3 of systemic blood pressure: 121/61 mean 83 mmHg and 677 dynes. Pulmonary angiogram showed normal size pulmonary artery branches, without filling defects, normal venous return to the left atrium and a left to right passage of contrast material through a small atrial septal defect.

Currently, the patient maintains a NYHA class I functional capacity, and is in treatment with acetylsalicylic acid 100 mg QD, sildenafil 12.5 mg BID and amlodipine 2.5 mg QD, without requiring supplemental oxygen.

DISCUSSION

Approximately, 40% of these congenital heart defects are associated to other cardiovascular anomalies,[2,3] such as: patent ductus arteriosus (75%), ventricular septal defects, aorto-pulmonary window, coarctation of the aorta, interrupted aortic arch, atrial septal defects, pulmonary vein stenosis. Accordingly, it is inferred that this condition is diagnosed at a young age; therefore, the case that we present shows a patient with this anomaly that remained relatively asymptomatic for a long time, which is unusual.

An association with CATCH 22 Syndrome has been found, including the Di George syndrome.[3] When the anomaly involves the left pulmonary artery, the congenital defect may be associated with tetralogy of Fallot.[4]

This condition must be diagnosed at an early stage, in order to perform a surgical correction at the appropriate time due to the high risk of developing an irreversible pulmonary vascular

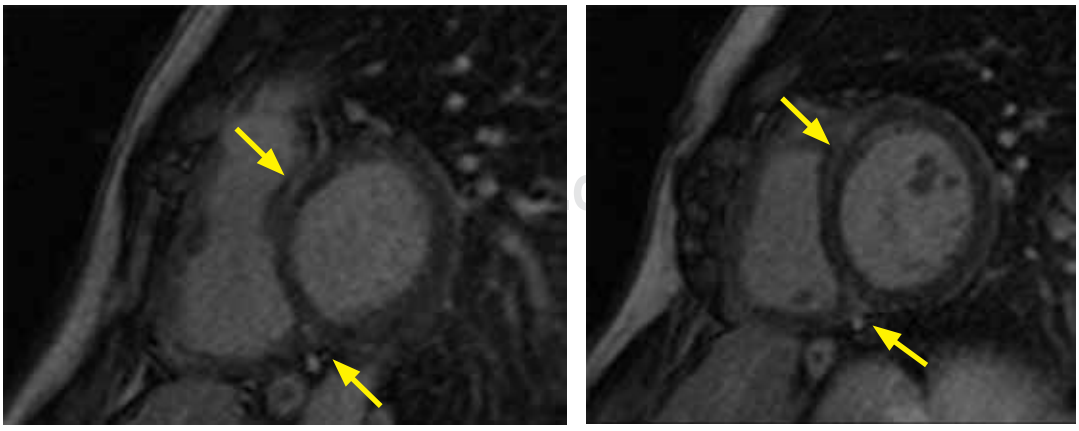

Figure 4:

Cardiac magnetic resonance (CMR) short axis view. Base **(A)** and mid-cavity **(B)** sections, showing a septal intra-myocardial late enhancement pattern, in relation to a non-ischemic pattern (yellow arrows).

disease. If it is not corrected at an early age, the survival rate reported could be as low as 30% at one year.[2]

Embryological pathology

The defect is caused by an incomplete migration of the right sixth aortic arch to the left. It can be the consequence of the lack of septation of the truncus arteriosus. The septation process starts with the emergence of two appendages in the primitive truncus, which will spread in a cephalic direction through the base of the conus and join with the conus septum. This septum will divide the aorta from the pulmonary trunk.[2] It is proposed that the anomalous origin of the pulmonary arteries could be related to a malposition of the Tandler's aorto-pulmonary septum, constituted by neural crest-derived mesenchymal cells. Normally, this septum has a right to left and dorsal to ventral orientation and separates the fourth aortic arch (located anterior and to the right and giving origin to the aortic arch) from the sixth aortic arch (located posteriorly and to the left, giving origin to the proximal portions of the pulmonary artery branches). The emergence of the right pulmonary artery from the aorta is caused by a leftward malposition of the aorto-pulmonary septum, while the anomalous origin of a left pulmonary artery from the aorta is caused by an abnormal position of this same septum to the right.[5]

Table 1: Intracavitary pressure record.

Anatomic site	Pressure in mmHg (millimetres of mercury)
LPA	50/25 mean 33
RV	50/4 end-diastolic 28
RA	Mean 4
RPA	120/80 mean 80
LV	120/ 80 D2 10

LPA = left pulmonary artery, RV = right ventricle, RA = right atrium, RPA = right pulmonary artery, LV = left ventricle, D2 = left ventricular end-diastolic pressure.

Classification

These types of defects are classified among the type III group of aorto-pulmonary septation defects. Usually originated at the posterolateral portion of the ascending aorta, in contrast with the presentation of our patient in whom it was

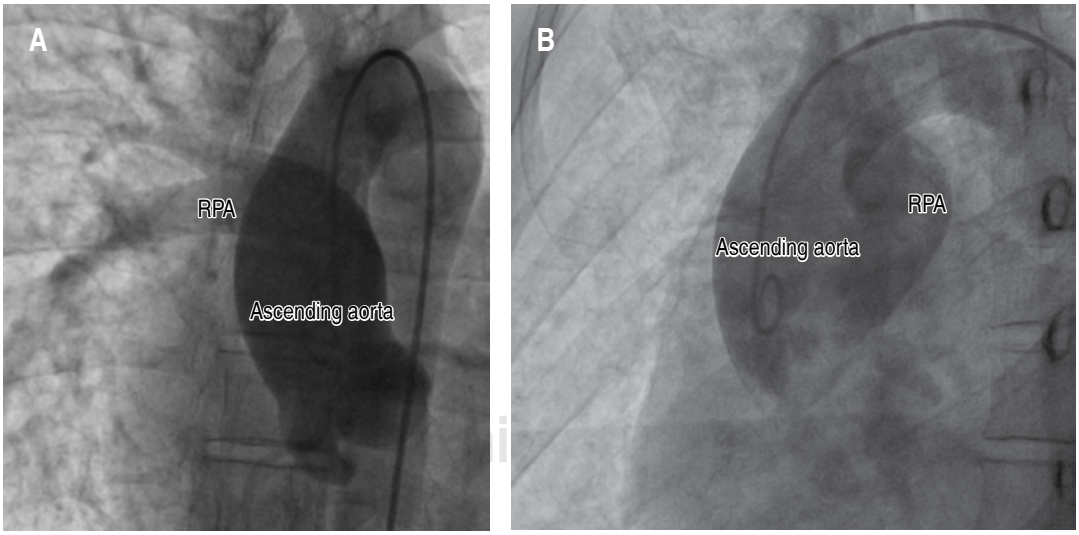

Figure 5: A. Aortography. Anteroposterior projection with caudal angulation. It is observed the presence of a 5fr pigtail catheter in the ascending aorta from a femoral access. Calling the attention the anomalous origin of the right pulmonary artery. **B.** Aortography. Left lateral projection with 90º angulation, where it is confirmed the anomalous origin of the right pulmonary artery from the posteromedial border of the ascending aorta.

originated at the posteromedial portion of the aorta. The origin of the right pulmonary artery can be located at different sites: proximal, with the origin at the ascending aorta, close to the aortic valve annulus; and distal, originated from the ductus arteriosus. Some other authors accept a third origin location close to the innominate artery.[3]

Pathophysiology

The abnormally connected lung is perfused at a systemic blood pressure, while the other is exposed to all the stroke volume coming from the right ventricle.[4] If a short-circuit is added from left to right, the hemodynamic situation gets even worse.[5]

After birth, with the fall in pulmonary vascular resistances, the flow to the anomalous pulmonary artery increases, causing a pulmonary overflow, leading to pulmonary hypertension.[4] Pulmonary hypertension developed in the lung irrigated by the main pulmonary artery could be caused by circulating vasoconstrictive substances or crossed neurogenic factors.[6]

CLINICAL PRESENTATION

Clinical manifestations include heart failure, cardiac murmurs, shortness of breath, tachypnea and frequent respiratory tract infections. Being heart failure the most prominent manifestation, and especially worst when associated with coarctation of the aorta or interrupted aortic arch.[7] Cyanosis may be present when pulmonary hypertension and vascular resistances are elevated.[2]

Diagnostic studies

The electrocardiogram can show signs of right ventricular hypertrophy.[2] Chest X-ray usually shows cardiomegaly and pulmonary flow redistribution, being more prominent on the side of the anomalous pulmonary artery.[2,8] An echocardiogram may show a posterior vessel that grows from the ascending aorta and perfuse the lung in the parasternal and suprasternal views.[2,9] Subcostal views could be useful if the pulmonary artery is originated from the lateral portion of the ascending aorta, but the most common origin is at the posterior portion of the aorta.[2,9] The anomaly may go unnoticed in up to 15% of the cases.[7]

Cardiac catheterization is only indicated in the evaluation of pulmonary vascular resistances in patients over six months of age.[6] A CT angiography and magnetic resonance angiogram (MRA) could also be used as complement studies when there is a high clinical suspicion and also to define the surgical treatment strategy.[10] Both cardiac catheterization and imaging studies such as CT angiogram and MRA represent helpful tools in the preparation of a corrective surgery and to asses prognosis, because they can contribute with important and precise anatomic details.

Prognosis and treatment

Due to the tendency to develop congestive heart failure on an early stage and irreversible pulmonary vascular disease, the prognosis is poor, often with a fatal outcome.[2] In the case of our patient, it draws the attention the fact that he became symptomatic late in his life.

The most commonly used surgical correction procedure is a direct anastomosis of the anomalous pulmonary artery to the main pulmonary trunk. A terminus-terminal anastomosis with the use of a synthetic graft can also be done, using a homograph patch or an autologous pericardial patch with the purpose of increasing the diameter of the anomalous pulmonary artery and avoid stenosis.[2] The most common postsurgical complication is the anastomosis stenosis (10.6%), a complication that could develop even months after surgery.[11] In these particular cases, re-operation is required, being the balloon dilation or a stent angioplasty the usual techniques.[11,12]

Without an early surgical correction, it is usually fatal, although, there are reports of late stage corrections.[13] Peng, et al. report a mortality close to 0%.[14] Among late complications after surgery, they described a stenosis of the anastomosis site (12.5%) and the need of a patch growth (12.5%).[14] Prifti, et al. mention a trans-operatory mortality around 20%, and 100% reoperation-free survival on late follow up.[15]

CONCLUSIONS

The congenital anomaly of the pulmonary artery is a rare condition, generally diagnosed at an early age as it can be associated with other cardiac defects, producing a more evident clinical presentation, although if isolated, it may remain unnoticed until adolescence and become an incidental finding on imaging studies.

In the case of our patient, we found the presence of a patent ductus arteriosus at a late age associated with the presence of the anomalous origin of the right pulmonary artery. Calling our attention is the fact that he remained with only a few and vague symptoms until a late time of life for this pathology. As part of the diagnostic approach, it is important to perform an echocardiogram, where these types of defects can be identified, and even more, to describe the hemodynamic impact on all cardiac chambers. Finally, a chest CT scan can be a useful diagnostic tool, and in order to describe in detail the anatomy of the pulmonary arteries, a MRA and cardiac catheterization with a pulmonary angiogram can be performed. This former procedure apart from a diagnosis confirmation, can be helpful to define the presence of pulmonary hypertension and also for hemodynamic and vasoreactivity assessment, with the purpose of a planned corrective surgery and long term prognosis. Due to its excellent outcomes, it is mandatory to perform an early surgical correction in order to avoid the progression of pulmonary vasculature disease to an irreversible condition, where it has an ominous prognosis and surgery is usually unsuitable.

In this particular case, the right pulmonary artery was redirected to the main pulmonary trunk, using a 16 mm woven Dacron tube and also, an 8 mm atrial septal defect was created with the purpose of reducing pressure on the right side of the heart due to the previous presence of pulmonary arterial hypertension. The intervention was an absolute success and the patient remains asymptomatic to date.

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Correspondence to:

Oscar Rene González-Hernández MD
Phone: 33 1384 3966
E-mail: oscar_vol76@hotmail.com

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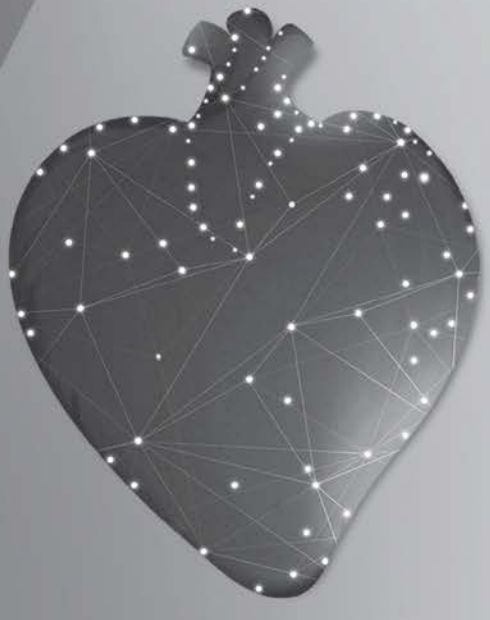

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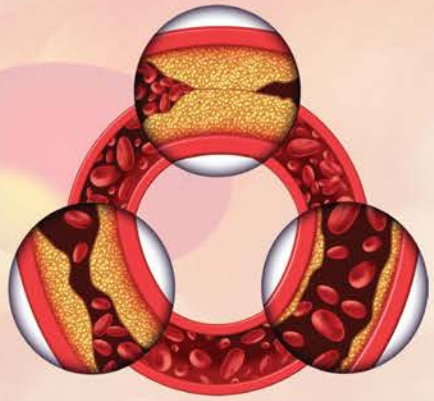

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