Journal of Advances in Medicine and Medical Research

32(4): 24-33, 2020; Article no.JAMMR.55030
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Evaluation of Heart Rate Variability in Critically-ill Neonates

Fatmah Nassar[1*], Ashraf Ibrahim[1], Amr Zoair[1] and Mohamed Rowisha[1]

[1]Faculty of Medicine, Tanta University, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author FN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AI, AZ and MR managed the analyses of the study. Author AZ managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i430396
Editor(s):
(1) Dr. Achour Radhouane, El Manar University of Tunis, Tunisia.
(2) Dr. Emin Umit Bagriacik, Gazi University, Turkey.
Reviewers:
(1) Fethi Ben Slama, National Institute of Public Health, France.
(2) John Ogedengbe, University of Abuja, Nigeria.
Complete Peer review History: http://www.sdiarticle4.com/review-history/55030

Original Research Article

Received 09 January 2020
Accepted 15 March 2020
Published 28 March 2020

ABSTRACT

Aims: The objective of this work was to evaluate heart rate variability (HRV) in critically-ill neonates admitted to NICU, to detect the effect of different causes of critical illness on cardiac autonomic function and outcome of these neonates.
Study Design: Case-control study.
Place and Duration of Study: Neonatal Intensive Care Unit (NICU) of Pediatric Department, Tanta University Hospital, in the period from January 2018 to May 2019.
Methodology: We included 30 neonates who were critically-ill according to Score for Neonatal Acute Physiology with Perinatal Extension II (SNAPPE-II score) as cases Group. Fifteen healthy full term neonates, matched for age and sex, were enrolled as a control group. 24-hour Holter monitoring was performed with recording and interpretation of ECG data for every neonate in the study, including analysis of HRV.
Results: There was significant increase of mean HR in critically-ill neonates as compared to control group. There was significant decrease of all HRV parameters (SDNN, SDANN, SDNNI, RMSSD and PNN50) in critically-ill neonates as compared to control group ($P < 0.05$). Significant negative correlations between SNAPPE-II score and HRV parameters (SDNN, SDANN, SDNNI,

**Corresponding author: E-mail: Fatimah_nassar@yahoo.com;*

RMSSD, PNN50) in critically-ill neonates were present, whereas there was non-significant positive correlation between SNAPPE-II score and mean heart rate.
Conclusion: HRV parameters decreased significantly in critically-ill neonates admitted to NICU, denoting severe cardiac autonomic dysfunction in these sick newborn infants. HRV strongly correlated to severity (SNAPPE-II score) and outcome, with strong relation to mortality of these critically-ill neonates.

Keywords: Neonates; SNAPPE-II; holter monitoring; HRV; critically-ill.

ABBREVIATIONS

HRV : Heart Rate Variability
ARF : Acute Renal Failure
BL : Birth Length
BSA : Body Surface Area
BW : Birth Weight
CT : Computerized Tomography
DIC : Disseminated Intravascular Coagulopathy
ECG : Electrocardiograp
GA : Gestational Age
HC : Head Circumference
HR : Heart Rate
IVH : Intraventricular Hemorrhage
MAS : Meconium Aspiration Syndrome
MODS : Multiple Organ Dysfunction Syndrome
NEC : Necrotizing Enterocolitis
NICU : Neonatal Intensive Care Unit
PNN50 : Percentage of differences between adjacent RR intervals that are greater than 50 m sec.
PPHN : Pulmonary Hypertension of Newborn
RDS : Respiratory Distress Syndrome
RF : Respiratory Failure
RMSSD : The square root of the mean squared differences of successive RR intervals
SDANN : The standard deviation of the average NN intervals calculated over short periods, usually 5 minutes of entire record.
SDNN : Standard deviation of all RR intervals
SDNNI : The mean of the standard deviations of all the NN intervals for each 5 min segment of a 24-h HRV recording

1. INTRODUCTION

The first few hours after admission to the neonatal intensive care unit (NICU) are critical for the high risk newborn babies in general, and preterm low birth weight infants in particular. Careful adherence to details in the delivery room and during the first few hours after birth is essential to help avoiding some of the immediate and long term complications. All staff should have a consistent approach to the initial care of these fragile infants upon admission to the neonatal unit [1].

Some factors that can place a baby at high risk and increase the chances of being critically-ill include; gestational age less than 34 weeks, birth weight less than 1.8 kg , after prolonged resuscitation, severe congenital anomalies , any newborn requiring surgery , newborn babies with cord pH less than 7.0 irrespective of gestation, hypoglycemia (if persistent despite oral feeds or if <1mmol/L), hyper-bilirubinemia requiring intensive phototherapy or likely to need exchange transfusion, unwell newborn e.g. respiratory distress, suspected sepsis, cardiac condition…etc., and infants with neonatal abstinence syndrome requiring treatment. Any newborn infant where close observation, continuous monitoring or active management is needed and where the neonatal team feels that he can't be provided safely on the postnatal ward or the transitional care area should be admitted to NICU.[1] Heart rate variability (HRV) has been used as a reliable method to detect cardiac autonomic nervous system activity. It represents a reliable reflection of the many physiological factors modulating the normal rhythm of the heart. HRV provides powerful means of observing the interplay between sympathetic and para-sympathetic nervous system. [2] Heart rate variability (HRV) is a measure of maturity of the autonomic nervous system and its ability to adapt to external events in neonates [3]. Determining the balance between the parasympathetic and sympathetic tones by assessing HRV in neonates is a useful measure of physiological stability. [4] Critically-ill neonates face many medical issues like breathing problems or congenital heart disease that may be seen in the neonatal intensive care unit (NICU). Stress during this period may be derived from physical stressors, neonate–mother separation, stressful medical conditions, and mechanical ventilation. Amongst the many physiological parameters to be monitored, HRV has not been thoroughly evaluated. Yet, it has been used in several

clinical conditions where severe amount of stress is present [5].

2. MATERIALS AND METHODS

Thirty (30) critically-ill neonates according to Score for Neonatal Acute Physiology with Perinatal Extension II (SNAPPE-II score) were enrolled in this study. They were chosen from critically-ill cases admitted at Neonatal Intensive Care Unit (NICU) of Pediatric Department, Tanta University Hospital, in the period from January 2018 to May 2019. They were 18 males and 12 females.

Fifteen (15) healthy full term neonates, matched for age and sex, were enrolled as a control group. They were 9 males and 6 females. Written informed consent was obtained from parents or guardians of subjects of the study. The study was approved by the Ethics Committee of Faculty of Medicine, Tanta University.

Inclusion criteria included critically ill neonates (neonatal sepsis, respiratory distress, prematurity (etc.) and therefore, admitted to NICU. SNAPPE-II score was used in assessment of critically-ill neonates admitted to the neonatal intensive care unit [6], SNAPPE-II score ≥ 30.

Exclusion criteria included, if vasoactive drugs were used during the first hour after admission, 5-min Apgar score of less than 4, skin temperature less than 35°C at any time after admission, neonates with cardiac arrhythmias or congenital heart diseases. All Neonates in this study were subjected to the following :(1) Complete history taking including.

Gestational age, early obstetric examination and ultrasound examination, problems during pregnancy, e.g. vaginal bleeding, illnesses during pregnancy, e.g. rubella, assessment of fetal growth and condition during pregnancy.

Spontaneous or induced onset of labour, method of delivery, signs of fetal distress and any problems during labour and delivery.

Apgar score and any resuscitation needed, any abnormalities detected, birth weight, head circumference and Vitamin K given. [2] Thorough clinical examination including:

Assessment of symptoms and signs of sepsis, prematurity, respiratory distress, SNAPPE-II score, heart rate and complete local cardiac examination. [3] Demographic data including:

Birth length, body weight, body surface area, head circumference and gestational age. [4] Investigations:

A. Routine laboratory investigations (required for critically-ill neonates):
B. Plain x-ray chest and heart and computerized tomography (CT) when indicated.
C. Echocardiography and Doppler (to assess cardiac function and exclude cardiac diseases).
D. Holter monitor: 24 Hour-Holter monitoring with recording and interpretation of ECG data for every neonate in the study, including analysis of HRV.

Ambulatory ECG (Holter monitoring) was used for analysis of heart rhythm and heart rate variability (HRV) over 24-hour period, using a Holter recorder device; Biomedical systems 300 (BMS 300), and Century Holter Analysis System C 3000 software (Biomedical systems, Louis, Belgium). The device was with three channels.

The recorder was a 5-lead patient cable which consists of 3 channels of ECG. The data were recorded while the neonate was admitted in the incubator, then all data were analyzed by computer. Any artefacts were removed.

3. RESULTS

We included 30 critically-ill neonates, 18 male and 12 female as a case group with a mean gestational age of 35.70 ± 2.52 weeks and mean weight of 2455.0 ± 629.2 g, whereas control group included 15 healthy neonates , 9 males and 6 females, with a mean gestational age of 37.0 ± 1.25 weeks and mean weight of 2640.0 ± 403.2 g. The critically-ill neonates included in case group were diagnosed as follows: 3 cases sepsis with necrotizing enterocolitis (NEC), 3 cases sepsis with acute renal failure (ARF), 5 cases respiratory distress Syndrome (RDS) with intraventricular hemorrhage (IVH), 2 cases respiratory failure with renal impairment, 2 cases hypoxia with multiple organ dysfunction syndrome (MODS), 3 cases severe sepsis with disseminated intravascular coagulopathy (DIC), 2 cases severe pneumonia with septicemia, 2 cases aspiration pneumonia, 2 cases severe persistent pulmonary hypertension of newborn (PPHN, 4 cases sepsis with liver failure and 2 cases meconium aspiration syndrome (MAS) with respiratory failure (RF) Table 2. There was no statistically significant difference between the

two groups with regards to gestational age, birth length, head circumference and weight (p > 0.05) Table 1.

The number of expired cases who died in this study was 19 out of the total number 30 critically-ill neonates with a percentage of 63.3%, having HRV parameters significantly lower and mean HR significantly higher than discharged ones who were 11 cases with a percentage of 36.7% Table 2.

In the present study, SNAPPE-II score has been used to identify critically-ill neonates, and it was 33.73±2.49 (range 30.0-39.0) in critically-ill neonates, whereas it was 2.53±2.88 (range 0.0-9.0) in the control group, with significant increase of SNAPPE-II score in critically-ill neonates as compared to control group (P < 0.05) Table 3.

Regarding mean heart rate and heart rate variability parameters, the mean HR in critically-ill neonates was 164.6 ±15.52 beats/min (range140.0-190.0 beats/min), whereas it was 127.4 ±11.55 beats/min (range 109.0-145.0 beats/min) in control group, with significant increase of mean HR in critically-ill neonates as compared to control group (P < 0.05).

As regards HRV parameters, SDNN in critically-ill neonates was13.30±9.64 m sec (range 2.0-31.0m sec), whereas it was 56.93±20.58 m sec (range 24.0-90.0 m sec) in control group, with significant decrease of SDNN in critically-ill neonates as compared to control group (P < 0.05).

SDANN was 10.13±6.91 m sec in critically-ill neonates (range 1.0-23.0 m sec), whereas it was 40.53±15.24 m sec (range 17.0-61.0 m sec) in control group, with significant decrease of SDANN in critically-ill neonates as compared to control group (P < 0.05).

Table 1. Demographic data of the studied groups

Demographic data	Critically-ill neonates (n=30)	Control (n=15)	T	P
GA (weeks)				
Min. – Max.	28.0 – 39.0	35.0 – 39.0	1.877	0.067
Mean ± SD.	35.70 ± 2.52	37.0 ± 1.25		
Median	36.0	37.0		
HC (cm)				
Min. – Max.	30.0 – 37.0	31.0 – 36.0	0.058	0.954
Mean ± SD.	34.10 ± 1.81	34.13 ± 1.81		
Median	34.0	35.0		
BL (cm)				
Min. – Max.	43.0 – 54.0	46.0 – 56.0	1.552	0.128
Mean ± SD.	48.20 ± 2.82	49.67 ± 3.31		
Median	48.0	49.0		
BW (g)				
Min. – Max.	900.0 – 3300.0	2100.0 – 3350.0	1.034	0.307
Mean ± SD.	2455.0 ± 629.2	2640.0 ± 403.2		
Median	2500.0	2500.0		
BSA (cm^2)				
Min. – Max.	389.8 – 724.0	574.9 – 737.3	1.237	0.223
Mean ± SD.	614.3 ± 83.52	643.2 ± 47.75		
Median	627.4	631.54		

T: Student t-test. P: p value for comparing between the two studied groups. GA: Gestational age. HC: Head circumference. BL: Birth length. BW: Body weight. BSA: Body surface area

Table 2. The number of preterm neonates was 13 out of the total number 30 of critically-ill neonates with a percentage of 43% of cases

	number	%	No. of expired cases
preterm	13	43%	8
Full term	17	56%	11

Table 3. Clinical diagnosis and outcome of critically-ill neonates

Clinical diagnosis	Critically-ill neonates	
	Number (n=30)	Percentage %
Sepsis with NEC	3	10%
Sepsis with ARF	3	10%
RDS with IVH	5	16.7%
RF with Renal Impairment	2	6.7%
Hypoxia with MODS	2	6.7%
Severe Sepsis with DIC	3	10%
Severe Pneumonia with Septicemia	2	6.7%
Aspiration Pneumonia	2	6.7%
Severe PPHN	2	6.7%
Sepsis with Liver Failure	4	13.3%
MAS with RF	2	6.7%
Outcome	**No. = 30**	**%**
Discharge	11	36.7
Expired (died)	19	63.3

SDNNI in critically-ill neonates was10.50±2.92 m sec (range 6.0- 15.0 m sec), whereas it was 36.47±17.20 m sec (range 11.0-64.0 m sec) in control group, with significant decrease of SDNNI in critically-ill neonates as compared to control group (P< 0.05).

RMSSD in critically-ill neonates was 8.13±4.62 m sec (range 1.0- 17.0 m sec), whereas it was 30.53±13.03 m sec (range 12.0-52.0 m sec) in control group, with significant decrease of RMSSD in critically-ill neonates as compared to control group (P<0.05).

PNN50 in critically-ill neonates was 0.46±0.28% (range 0.0- 0.90%), whereas it was 18.47±11.83 % (range 0.0-34.0%) in control group, with significant decrease of PNN50 in critically-ill neonates as compared to control group (P<0.05) Table 4.

There were significant negative correlations between SNAPPE-II score and HRV parameters (SDNN, SDANN, SDNNI, RMSSD, PNN50) in critically-ill neonates (P<0.05). There was non-significant positive correlation between SNAPPE-II score and mean HR (P>0.05) Table 4 and Figs. 1 and 2.

Figs. 1-2 show that there were significant negative correlations between SNAPPE-II score and HRV parameters (SDNN, SDANN) in critically-ill neonates.

The mean HR in critically-ill neonates who were discharged from NICU was 154.50±11.83 beats/min (range 140.0- 173.0 beats/min), whereas it was 169.65±14.85 beats/min (range 140.0-190.0 beats/min) in neonates who expired, with significant increase of mean HR in critically-ill neonates who died as compared to those who were discharged alive from NICU (p<0.05).

Regarding comparison of HRV parameters (SDNN, SDANN, SDNNI, RMSSD, PNN50) between the two groups and their relation with the outcome , there was significant decrease of HRV parameters in critically-ill neonates who were expired as compared to those who were discharged alive from NICU (p<0.05) Table 6.

4. DISCUSSION

In the normal fetus and newborn, the heart rate varies as a result of the balance between sympathetic and parasympathetic impulses to the Sino-atrial node, originating mainly in the cardio-regulatory centers in the medulla under the modifying influences of the higher centers [7].

The present study aimed to evaluate heart rate variability (HRV) in critically-ill neonates admitted to NICU, to detect the effect of different causes of critical illness on cardiac autonomic function and outcome of these neonates.

In the present study, SNAPPE-II score has been used to identify critically-ill neonates, and it was significantly higher in these patients as compared to controls (≥30).

According to Mia et al. [8], the cut-off value of SNAPPE-II score of the critically-ill neonates was 30 or above.

Moreover, SNAPPE-II score was higher among expired neonates as compared to survived ones.

A mean score of 37 was associated with higher mortality. However, it didn't accurately predict the length of stay in NICU [6].

In this study, HRV has been measured in critically-ill neonates associated with sepsis, prematurity, respiratory distress, hypoxia and others, by 24 hour-Holter monitoring. According to the results of this study, it was found that there was significant increase of mean HR and significant decrease of all HRV parameters in critically-ill neonates as compared to controls.

Table 4. Comparison between the two studied groups according to SNAPPE-II score

SNAPPE-II	Critically-ill neonates (n=30)	Control (n=15)	P
Min. – Max.	30.0 – 39.0	0.0 – 9.0	<0.001*
Mean ± SD.	33.73 ± 2.49	2.53 ± 2.88	
Median	34.50	1.0	

Table 5. Comparison between the two studied groups according to Heart Rate Variability (HRV) by Holter monitor

Heart rate variability	Critically-ill neonates (n=30)	Control (n=15)	Test of sig.	P
Mean HR (beat/min)				
Min. – Max.	140.0 – 190.0	109.0 – 145.0	t = 8.200	<0.001*
Mean ± SD.	164.6 ± 15.52	127.4 ± 11.55		
Median	165.0	126.0		
SDNN (m sec)				
Min. – Max.	2.0 – 31.0	24.0 – 90.0	U= 9.0	<0.001*
Mean ± SD.	13.30 ± 9.64	56.93 ± 20.58		
Median	10.50	57.0		
SDANN (m sec)				
Min. – Max.	1.0 – 23.0	17.0 – 61.0	U= 10.50	<0.001*
Mean ± SD.	10.13 ± 6.91	40.53 ± 15.24		
Median	8.50	42.0		
SDNNI (m sec)				
Min. – Max.	6.0 – 15.0	11.0 – 64.0	U= 15.0	<0.001*
Mean ± SD.	10.50 ± 2.92	36.47 ± 17.20		
Median	10.50	35.0		
RMSSD (m sec)				
Min. – Max.	1.0 – 17.0	12.0 – 52.0	U= 10.0	<0.001*
Mean ± SD.	8.13 ± 4.62	30.53 ± 13.03		
Median	8.0	29.0		
PNN50 (%)				
Min. – Max.	0.0 – 0.90	0.0 – 34.0	U= 29.50	<0.001*
Mean ± SD.	0.46 ± 0.28	18.47 ± 11.83		
Median	0.45	20.0		

Table 6. Correlation between SNAPPE-II score and HRV in Critically-ill neonates

Heart Rate Variability (HRV) parameters	SNAPPE-II score	
	R_s	P
Mean HR	0.344	0.062
SDNN	-0.414	0.023*
SDANN	-0.403	0.027*
SDNNI	-0.406	0.026*
RMSSD	-0.400	0.028*
PNN50	-0.423	0.020*

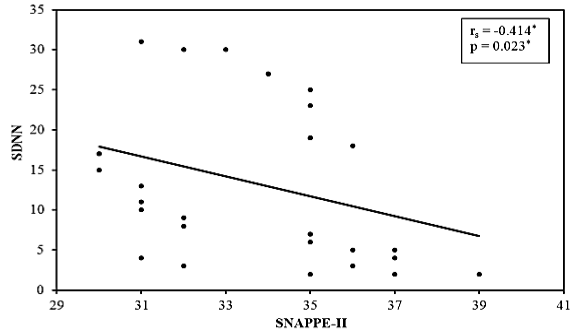

Fig. 1. Correlation between SNAPPE-II score and SDNN in Critically-ill neonates

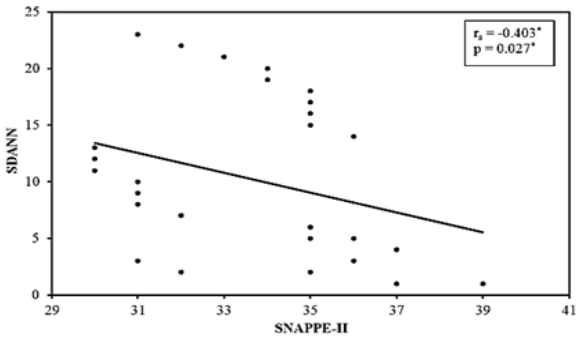

Fig. 2. Correlation between SNAPPE-II score and SDANN in Critically-ill neonates

Table 7. Relation between outcome and Heart Rate Variability (HRV) in Critically-ill neonates

HRV	Outcome (n=30)		Test of sig.	P
	Discharge (n= 11)	Expired (n= 19)		
Mean HR (beat/min)				
Min. – Max.	140.0 – 173.0	140.0 – 190.0	T = 2.804*	0.009*
Mean ± SD.	154.50 ± 11.83	169.65 ± 14.85		
Median	152.50	168.0		
SDNN (m sec)				
Min. – Max.	6.0 – 31.0	2.0 – 30.0	U = 36.50*	0.004*
Mean ± SD.	20.40 ± 8.47	9.75 ± 8.25		
Median	20.0	7.0		
SDANN (m sec)				
Min. – Max.	5.0 – 23.0	1.0 – 22.0	U = 37.50*	0.005*
Mean ± SD.	15.0 ± 5.87	7.70 ± 6.15		
Median	15.0	6.0		
SDNNI (m sec)				
Min. – Max.	9.0 – 15.0	6.0 – 15.0	U = 37.0*	0.005*
Mean ± SD.	12.60 ± 1.96	9.45 ± 2.78		
Median	12.50	9.0		
RMSSD (m sec)				
Min. – Max.	5.0 – 17.0	1.0 – 16.0	U = 39.50*	0.006*
Mean ± SD.	11.30 ± 3.59	6.55 ± 4.31		
Median	11.0	6.0		
PNN50 (%)				
Min. – Max.	0.30 – 0.90	0.0 – 0.90	U = 37.0*	0.005*
Mean ± SD.	0.66 ± 0.20	0.36 ± 0.26		
Median	0.65	0.30		

T: Student t-test. U: Mann Whitney test. P: p value for relation between outcome and Heart rate variability

This is in agreement with Thayer et al. [9] and Coggins et al. [10], who reported that critically-ill neonates have severe dysfunction of the autonomic nervous system that leads to attenuation of all parameters of HRV.

Heart rate variability has been studied by Jenkins et al. [11] in a group of 66 newborn infants for periods of up to 72 hours from birth. HRV was reduced in infants suffering from idiopathic respiratory distress syndrome, and this was more marked with severe respiratory distress requiring mechanical ventilation. Persistent reduction in heart rate variability was associated with increased mortality. The results of this study suggest that reduction in heart rate variability is a consistent finding in severe idiopathic respiratory distress syndrome, and, if persistent, usually indicates poor prognosis. Reduction in HRV may be due to high levels of sympathetic activity, which is the cause of increase of HR in these patients.

Selig et al. [12] conducted a research on forty-eight premature neonates with different gestational ages who had their heart rates assessed and HRV obtained by recording RR intervals. HRV was analyzed according to time (SDNN, RMSSD and SD1/SD2) and frequency (VLF, LF, HF and LF/HF). Preterm neonates were compared with a group of 78 healthy near-term neonates with no perinatal events. They concluded that preterm neonates have less complex heart rate variability behavior than term neonates, which was evident in time and frequency domains. This should be interpreted as indicative of minor neurological development, since preterm infants showed significantly smaller variability than the normal neonates. The study of HRV in this group can be considered another tool in the evaluation of autonomic maturation and hence the progression to normality.

In agreement with our results, Bohanon et al. [13] showed that HRV measurements in time-domain and HR were significantly different in septic patients versus non-septic controls. They concluded that nonconventional vital signs such as HRV are highly sensitive in the confirmation of sepsis in neonates. HRV may allow for earlier identification of septic physiology.

Also, Kero [14] recorded heart rate, short-term heart rate variability, long-term heart rate variability, mean arterial blood pressure and R-to-pulse time in 28 neoborn infants during the acute phase of respiratory distress syndrome (RDS). The patients were classified by a clinical scoring system into three classes related to the severity of the disease. The HRV was initially significantly lower in infants with severe RDS (class III) than in those with moderate or mild disease (classes II and I). Only in class III, the HRV increased significantly during recovery.

Beat to beat variation in heart rate are the result of complex interactions of respiration, blood pressure, vasomotor tone, body temperature and higher cortisol output, primarily mediated through the central nervous system. Efferent control of heart rate is through the autonomic nervous system. Sympathetic input acts to increase heart rate, while parasympathetic input slows the heart rate. Accentuated antagonism refers to the variable effect of input from one limb of the autonomic nervous system depending upon the input from the opposing limb. Age, position, activity, level of arousal and emotional state modulate these interactions [15].

A secondary outcome was investigated in this study regarding the correlation between SNAPPE-II score and HRV in critically-ill neonates, showing that there was significant negative correlation between SNAPPE-II score and all HRV parameters and non-significant positive correlation between SNAPPE-II score and mean HR. These results are in agreement with Lim and Rozycki [16].

The number of expired cases who died in this study was 19 out of the total number 30 critically-ill neonates with a percentage of 63.3%, having HRV parameters significantly lower and means HR significantly higher than discharged ones who were 11 cases with a percentage of 36.7%. This is in accordance with Griffin [17], who reported that abnormal heart rate characteristics (HRC) of reduced variability and transient decelerations occur early in the course of neonatal sepsis. Algorithms has been developed to detect these HRC, and showed significant association of them with sepsis and with death.

Critically-ill neonates according to SNAPPE-2 score and HRV parameters regardless to the main cause of being critically-ill. However further studies are suggested on larger groups of critically-ill neonates to evaluate if there is a statistically preponderant correlation between certain pathologies and Heart rate variability (HRV) parameters much more than others.

5. CONCLUSION

Heart rate variability (HRV) parameters decreased significantly in critically-ill neonates admitted to NICU, denoting severe cardiac autonomic dysfunction in these sick newborn infants.

HRV strongly correlated to severity (SNAPPE-II score) and outcome, with strong relation to mortality of these critically-ill neonates.

CONSENT

All authors declare that 'Written informed consent was obtained from parents or guardians of subjects of the study. The study was approved by the Ethics Committee of Faculty of Medicine, Tanta University.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. O'Reilly H. Trust guidelines for admission of newborn babies to the Neonatal Unit. CGAP. 2015;3:1-12.
2. Silvilairat S, Wongsathikun J, Sittiwangkul R, Pongprot Y, Chattipakorn N. Heart rate variability and exercise capacity of patients with repaired tetralogy of Fallot. Pediatr Cardiol. 2011;32:1158–1163.
3. Groome LJ, Loizou PC, Holland SB, Smith LA, Hoff C. High vagal tone is associated with more efficient regulation of homeostasis in low-risk fetuses. Developmental Psychobiology. 1999;35: 25–34.
4. Javorka K, Lehotska Z, Kozar M, Uhrikova Z, Kolarovszki B, Javorka M, Zibolen M. Heart rate variability in newborns. Physiol Res. 2017;66:S203-S214.
5. Faye PM, De Jonckheere J, Logier R, Kuissi E, Jeanne M, Rakza T, Storme L. Newborn infant pain assessment using heart rate variability analysis. The Clinical Journal of Pain. 2010;26:777-82.
6. Harsha S, Archana B. SNAPPE II as a predictor of mortality and morbidity. Journal of Clinical and Diagnostic Research. 2015;9:10-12.
7. Yeh S, Forsythe A, Hon EH. Quantification of fetal heart beat-to-beat interval differences. Obstetr Gynecol. 1973;41:355.
8. Mia, RA, Etika R, Harianto A, Indarso F, Damanik SM. The use of score for neonatal acute physiology with perinatal extention II (SNAPPE II) in predicting neonatal outcome in neonatal intensive care unit. Paediatrica Indonesiana. 2005; 45:241- 45.
9. Thayer JF, Shelby SY, Jos FB. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. International Journal of Cardiology. 2010;141(2):122-131.
10. Coggins SA, Weitkamp JH, Grunwald L, Stark AR, Reese J, Walsh W, Wynn JL. Heart rate characteristic index monitoring for bloodstream infection in NICU: A 3-year experience. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2016;101(4):329-332.
11. Jenkins JG, Reid MM, McClure BG. Study of heart rate variability in sick newborn infants. Acta Paediatr Scand. 1980;69(3): 393-396.
12. Selig FA, Tonolli ER, Silva EV, Godoy MF. Heart rate variability in preterm and term neonates. Arq Bras Cardiol. 2011;96(6): 443-9.
13. Bohanon FJ, Mrazek AA, Shabana MT, Mims S, Radhakrishnan GL, Kramer GC, Radhakrishnan RS. Heart rate variability analysis is more sensitive at identifying neonatal sepsis than conventional vital signs. The American Journal of Surgery. 2015;210(4):661–667.
14. Kero P. Heart rate variation in infants with the respiratory distress syndrome. Acta Paediatr Scand. 1974;250: 1-70.
15. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart

rate variability. Frontiers in Psychology. 2014;5:1040.

16. Lim L, Rozycki HJ. Postnatal SNAPPE-II scores in neonatal intensive care unit patients: Relationship to sepsis, necrotizing enterocolitis and death. J Matern Fetal Neonatal Med. 2008;21:415-9.

17. Griffin MP. Heart rate characteristics: Novel Physiomarkers to predict neonatal infection and death. Pediatrics. 2005;116 (5):1070–1074.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/55030