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Caffeine Effect as Confounding Factor in Sepsis Diagnosis by Heart Rate Signal Processing

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Abstract

Objectives: Apnea leads to respiratory arrest in premature infants, which decreases through the administration of caffeine by increasing the heart rate (HR). Nowadays, using electrocardiogram (ECG) signals, along with studying and comparing heart rate characteristics (HRC) in premature infants is considered as the most critical claim in the early detection of diseases, especially sepsis. Accordingly, this study investigated the effect of caffeine on HRC.

Materials and Methods: To this end, the raw ECG data of infants were collected from the Akbarabadi neonatal intensive care unit section and then processed in time and statistical domain. Next, the effect of caffeine on their HRC was investigated, and finally, HRC signals were analyzed fifteen minutes before and immediately after caffeine administration.

Results: Before caffeine administration, the probability distribution of inter-beat (RR) intervals and the probability distribution of the R_2/R_1 ratio were close to the normal distribution. According to previous studies, the irregularity of the signal in the diagram of the beat to beat RR interval indicates the infant health. However, these diagrams showed an abnormal distribution, and a specific uniformity was observed in the RR interval diagram after the administration of caffeine.

Conclusions: Based on the results of this study, changes in the infant's HRC and its pattern should be identified after drug administration in order to evaluate the status of newborns, primarily through new methods of sepsis prediction in preterm infants. Eventually, the findings of this study enable clinicians to consider the drug effect as a confounding factor with a specific pattern in the signal without disconnecting diagnostic devices from infants for drug administration.

Keywords: Caffeine, Sepsis, Diagnoses, Signal processing

Introduction

Apnea causes respiratory arrest in premature infants, which, in turn, results in oxygen deficiency and subsequent problems such as brain and heart damage. On the other hand, caffeine administration prevents apnea in premature infants (1,2). More precisely, it significantly changes the infant's heart rate (HR). These changes happen so quickly that they are demonstrated as an increase in the HR in monitors immediately after drug administration. Research has revealed that premature infants have a specific heart characteristic and pattern according to disease type (3).

One of the new solutions in prognostic in premature or very low birth weight (VLBW) infants is the use of signal processing techniques. Signal processing can be in time, frequency, statistics domain, or a combination of them (4). Sepsis is one of the diseases that causes a high rate of infant mortality, especially in premature infants. That is why early detection is highly important in treating VLBW or premature infants (5). Recently, many studies have focused on the early detection of infection through heart rate characteristics (HRC) changes. Experts are extremely sensitive to the early prognosis of sepsis in premature infants by observing changes in the processed signals. In addition to infections, other diseases can be detected by examining different patterns in HRC changes, but sepsis is the most common one (6).

However, what is remarkable about this research is investigating the effects of drugs that affect the rhythm of the premature infant's HR (7). In this study, a question was raised regarding whether drugs can change the HRC of premature infants. The effect of the drug can interfere with the early diagnosis of the disease if these changes are significant. To this end, premature infants' electrocardiogram (ECG) raw data were collected in the neonatal intensive care unit (NICU) of Akbar Abadi Hospital. In addition, infants who were free of infections but were taking caffeine because of their apnea were isolated in this valuable study. Then, the ECG signal of a baby who was only taking the drug and was free of sepsis was evaluated to find if looking at HRC changes can be an excellent guide to the prognoses of sepsis.

Therefore, with the advancements in the identification

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of patterns through fuzzy logic and artificial intelligence, hospital devices are expected to identify the pattern of drug effects on infants' HR in addition to the identification of tachycardia and bradycardia patterns (8, 9).

Considering the above-mentioned explanations, this study intended to find the most varied HRC due to caffeine administration. This research can help to develop a mathematical model for identifying this pattern for future works. After identifying and modeling, the effect of such phenomena can be considered as a confounding factor in the data collecting system and then be eliminated. Therefore, identifying significant changes in HRC is essential.

Materials and Methods

There are 25 beds equipped with data monitoring and recording systems at Akbarabadi Hospital. Therefore, using a large sample of a limited population (n = 25), 20 infants were randomly selected with *P* = 0.85, a 95% confidence level ($Z_{1-\alpha/2}$= 1.96), and 5% accuracy (d = 0.05) for this test.

Of these 20 infants, 15 cases were approved for respiratory apnea problems in one week. Of these 15 infants, nine cases had sepsis in addition to apnea. In addition, three infants were detected with intraventricular hemorrhage (IVH) and two infants had other diseases such as respiratory distress syndrome and a combination of illnesses with their apnea problem. The obtained valuable sample in this study was an infant who was hospitalized only for his apnea and received caffeine administration, and his ECG data were precious for signal analysis. Further, caffeine was the only cause of HRC changes in the infant's HR in this study. The present study aimed to investigate the net effect of the drug on HRC.

Therefore, this study examined the real effect of the drug alone on HRC three times before and after drug injection.

In this respect, a 31-week-old premature infant in the NICU of Akbarabadi hospital in Tehran (September 2019 until February 2020) was selected, who was receiving caffeine in order to prevent apnea. The ECG signals were recorded 15 minutes before and after drug administration, and then analyzed based on the algorithms of HRC analysis for sepsis detection in premature infants like the HeRO score. Next, some monitors (Pooyandegan Raheh Saadat Company) were used that could store the desired data for offline processing. The data of ECG signals were collected with a frequency of 200 Hz, allowing the device to store up to 24 hours of data in its central system and send them to external memory for analysis. Therefore, the implementation of this project caused no interference in the treatment process of newborns.

An infant without proven sepsis receiving caffeine in order to prevent apnea was selected based on the HeRO score of sepsis reported in the literature.

Next, the infant received caffeine at 9:00 AM. A sample of the heart signal was recorded at about 5 AM before drug administration to extract the status of HRCs. Considering that the infant received other medications in addition to caffeine, ECG signals were recorded after the peak onset of other medications in order to minimize confounding effects on caffeine.

To increase the accuracy of the study and decrease the confounding factors of other drugs, HR signals were recorded four hours before caffeine administration. The determined time for caffeine administration was 9 AM. Furthermore, the signals were recorded at 5 O'clock AM for 15 minutes, and then heart signals were recorded for 15 minutes immediately after caffeine administration. Finally, these two data were compared to know if caffeine can significantly increase heart variabilities. If the variability is significant, it may mislead experts in the early diagnosis of sepsis or IVH by signal processing. The variables of analyzed ECG signals were as follows:

The Inter-beat (RR) interval and beat number: This is one of the essential characteristics for the evaluation of HRC. As shown in Figure 1, an irregular diagram indicates that the person is healthy, and a specific regularity in this signal means that the duration between each of Rs tends to a specific value, indicating a type of problem in the infant (10).

Sample Asymmetry (SampAs) or R_2/R_1 Ratio (Time domain): The R_1 and R_2 criteria represent the high and low medians of the signal in the RR interval, respectively. Equations (1) and (2) show these numbers. Suppose there are n points (x_1, x_2, ..., x_i, ..., x_n) in each RR interval and their median is m, therefore:

$$R_1 = \frac{1}{n}\sum_{i=1}^{n} \min(x_i - m, 0)^2 \quad (1)$$

$$R_2 = \frac{1}{n}\sum_{i=1}^{n} max\ (x_i - m, 0)^2 \quad (2)$$

R_2/R_1 ratio (*SampAs*) demonstrates the number of signal irregularities in the RR interval (11). Moreover, the statistical probability distribution for a healthy infant should be reasonable. However, deviation from a normal distribution (decelerations) indicates a problem in the newborn. Thus, the evaluation of this factor is of particular importance for prognosis. The similarity of this pattern after receiving caffeine with other patterns may lead to an error in prognosis (10).

The Statistical Distribution of the Duration of RR Interval (Statistical Criteria): For a more accurate evaluation of RR intervals, the histogram of RR intervals was plotted, indicating changes during 15 minutes before and after caffeine administration. This longer time interval in the diagram allows us to obtain more accurate results from the HRC analysis thus it was compared with the HeRO pattern in sepsis. This diagram displays regularities and irregularities in RR intervals. In Figure 2, the left chart shows a frequency distribution of the samples number calculated between each R peak for a healthy infant and the right one pertains to the frequency distribution of a sick infant.

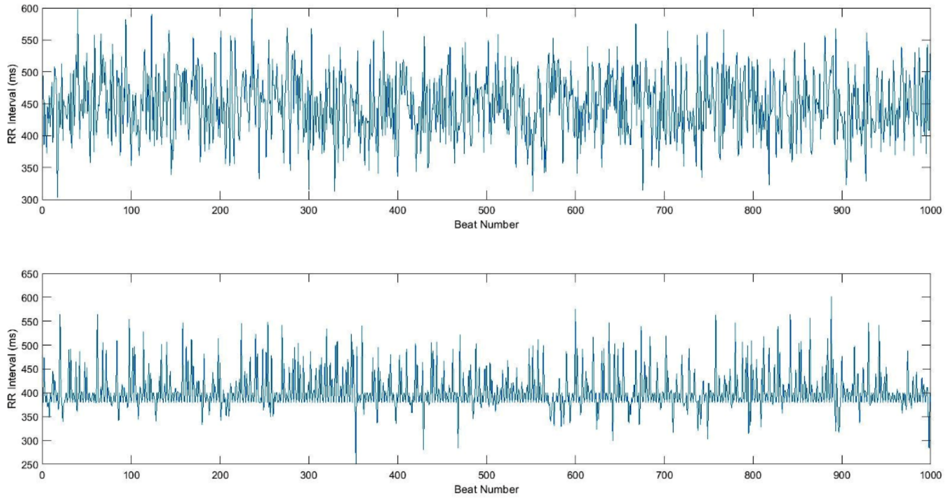

Figure 1. The Above Diagram With Irregularities in the RR Interval Pertains to a Healthy Infant. *Note*. IVH: Intraventricular hemorrhage; This diagram with a particular regularity is associated with an unhealthy infant diagnosed with sepsis or IVH or apnea.

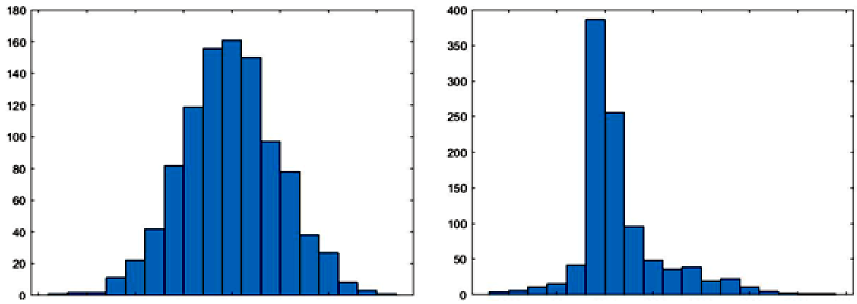

Figure 2. The Asymmetry Number is a Sign of Irregularity in the RR Interval Signal.

The evaluation of these factors helps investigate the effect of caffeine on each HRC and find the characteristic which is most affected by this drug.

Results

Table 1 presents the demographic features of the newborn. As described in the method section, the sample signals of the infant were stored and analyzed in MATLAB 2018. Figure 3 shows the infant's heart signal obtained from ECG without any analysis. Only the identified peak points are marked.

Table 1. Characteristics of the Newborn at Birth

City	Tehran
Gender	Male
First minute Apgar	8
Fifth minute Apgar	10
Delivery method	Cesarean section
Gestational age	31 weeks
Birth weight	900 g
Receiving surfactant	No
Resuscitation	PPV
Gestation number	G1P1AB0

The diagram of the RR interval (ms) versus the beat number for ten minutes of each experiment is illustrated in Figure 4. As shown, the diagram is considered a healthy sample (irregular) before caffeine administration, and the RR interval varies between 400 and 500 ms. However, the RR interval tends to a specific number (about 400 ms) after caffeine administration. As expected, HR increased after the administration of caffeine. Long duration and close to zero data arise from both noises in the received information and diagnosis error in the identification algorithm of the R peak. Therefore, about ten minutes of this signal are displayed for demonstrating the generality addressed in the discussion in order to observe time fluctuations between R peaks and to reduce the noise effect in analyses.

Figure 3 depicts the histogram of the RR interval statistical distribution 15 minutes before and after caffeine administration. RR interval varies between 400 and 500 ms. However, after caffeine administration, the RR interval tends to a specific number (about 400 milliseconds). This statistical distribution shows changes in HRC and can be a good indicator of the drug effect.

Similarly, Figure 6 illustrates the frequency data of the

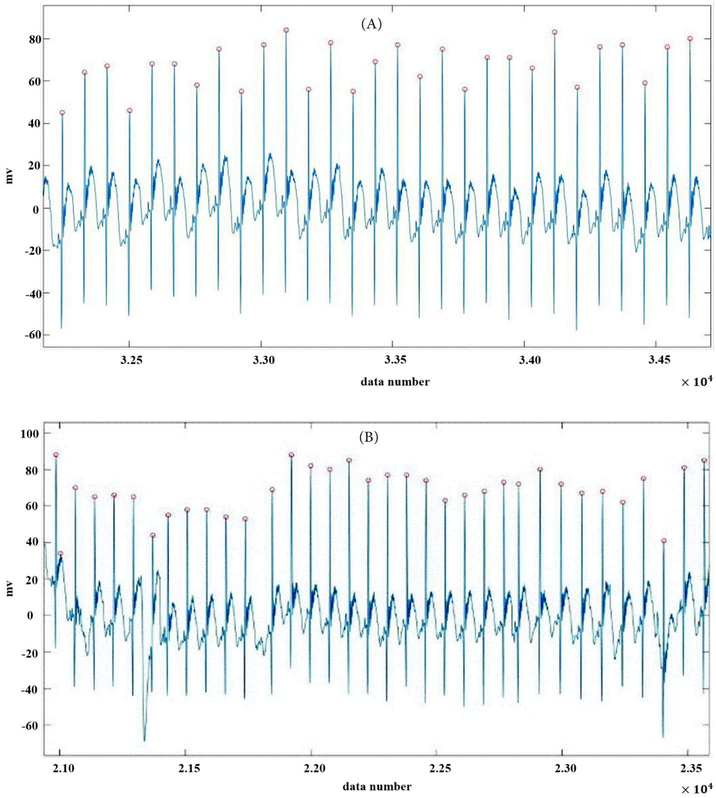

Figure 3. The Heart Signal Sample of the Infant Before (A) and After (B) Administration of Caffeine

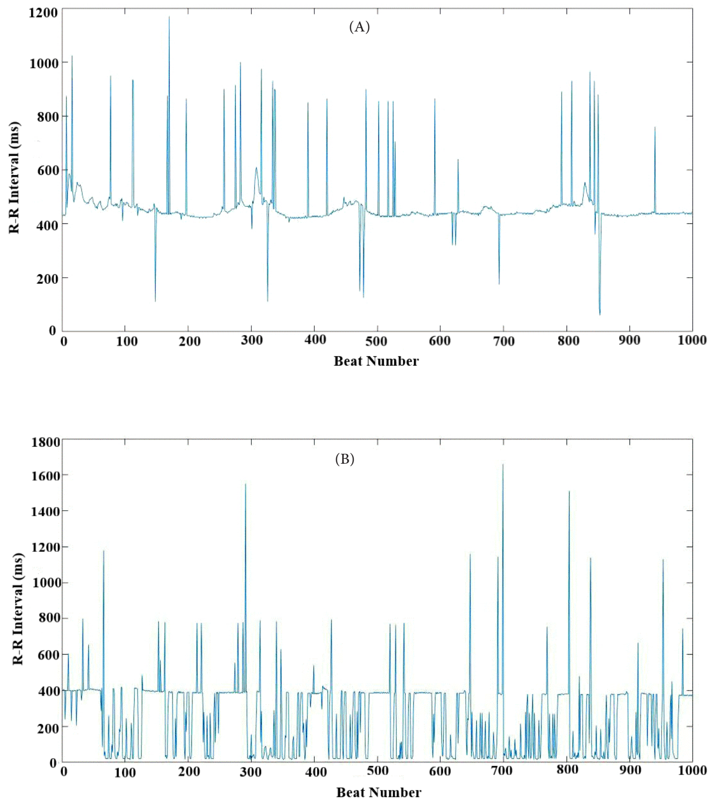

Figure 4. Diagram of RR Interval Versus Beat Number Before (A) and After (B) Caffeine Administration for About 10 Minutes.

same period for the signals of Figure 5. The sample shows asymmetry numbers during this time. Based on these graphs, this ratio had a reasonably normal distribution and was less than 0.03 before administration. However, as R_1 and R_2 changed, the data changed in two parts (i.e., less than 0.02 and 1.2) after administration.

Discussion

As mentioned earlier, there have been various research on neonatal HRC changes for the prognosis of diseases in premature infants, especially in the issue of the early detection of sepsis. Projects such as determining the HeRO number, which is an example of new activities by artificial intelligence and signal processing techniques, have recently helped experts for early detection in this regard. This number is obtained by changing the HRC in infants. To this aim, the chest lead is usually be attached to the baby and the ECG data are sent to the device for analysis, and then the device announces a number for HRC changes. Signal processing through the HeRO score in NICUs has gained particular importance, which is the result of the HRC analysis (12, 13).

Although valuable research has been conducted around the world for the early detection of any kind of disease implementing ECG data analysis, some studies have focused on the effect of the drug on HRC. Therefore, this study presented an example of the confounding factor on HRC and determined the HeRO number.

Once the infant's HRC is affected by the drug, an error is expected in the prognosis and its application (14,15). In this study, a newborn without sepsis receiving caffeine for the prevention of apnea was selected after observing infants in Akbar Abadi Hospital of Tehran. The absence of sepsis is essential since HeRO score studies have shown that HRC, obtained through the evaluation of ECG signals, changes in infants with sepsis (16). The effect of medication alone on infants without sepsis is significant for the development and enhancement of engineering prognosis precision (17).

Aminophylline and caffeine were first introduced in 1995 in order to prevent apnea and bradycardia in neonates. The results of this study showed that neonates who received caffeine had a lower median HR compared to the group receiving aminophylline, indicating that caffeine is more appropriate for newborns (18). Although the effect of caffeine on HR is lower than that of aminophylline, a question arises whether these changes can affect the HRC analysis for an infant.

Some studies have especially focused on this issue. For example, Cummings investigated the effect of caffeine on infants through HRC analysis and found that caffeine could help the survival of infants who were prone to

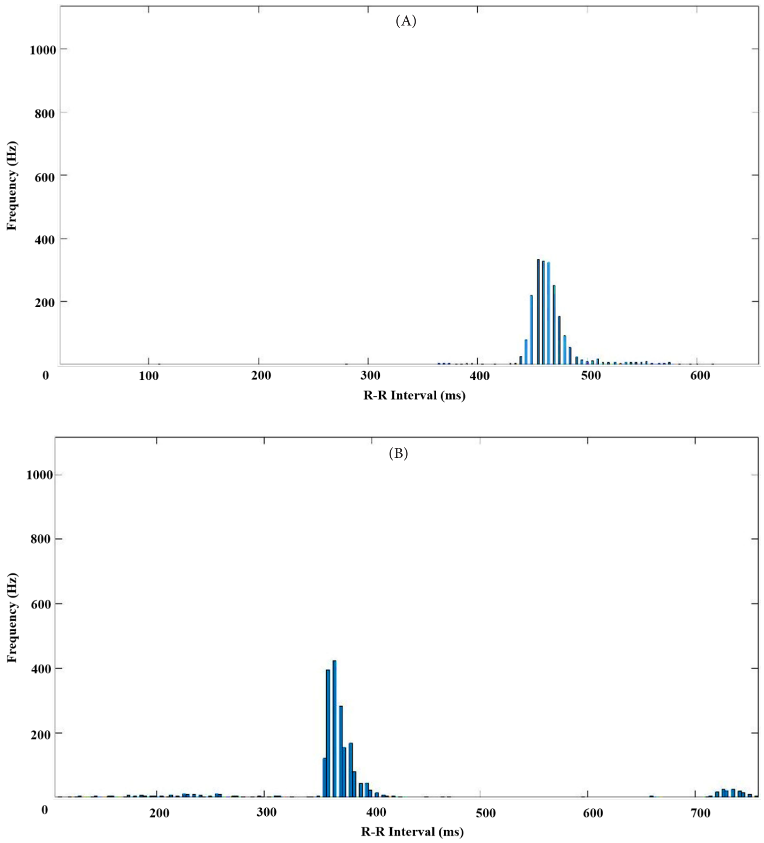

Figure 5. Histogram of RR Interval Frequency 4 Hours Before (A) and Immediately After (B) Administration of Caffeine. Note. RR: Inter-beat.

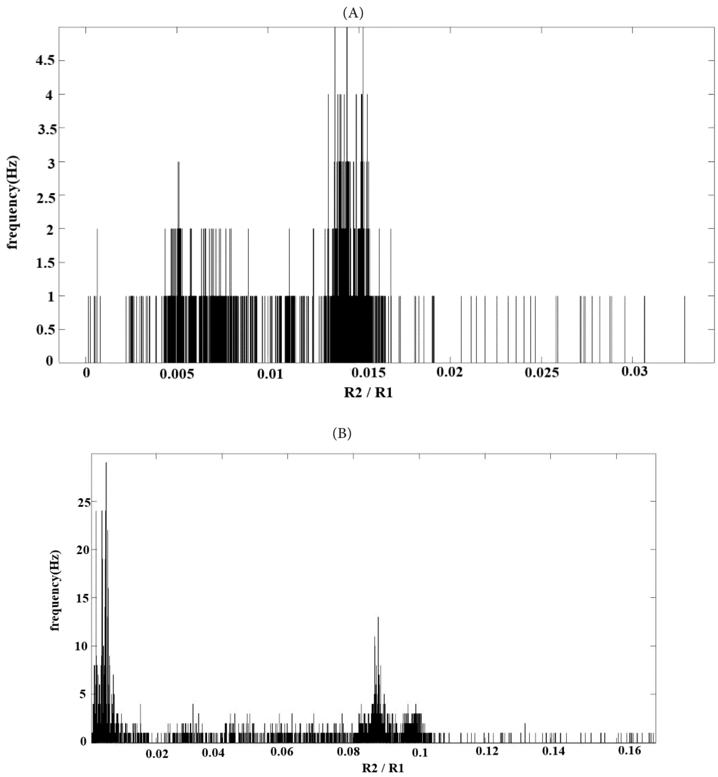

Figure 6. Frequency Distribution of R_2/R_1 Before (A) and After (B) Administration of Caffeine.

respiratory arrest. Moreover, this drug had a highly positive impact on HRC (19).

In addition, Koenig et al studied the effect of drinking caffeine on HRC in adults. In this review article, which also included the authors' experiments, they reported that the effect of caffeine on HRC requires vast investigation, and its impact is unclear (20).

Further, Ulanovsky et al evaluated the impact of caffeine on newborns and reported that the drug failed to affect HRC in infants (21). However, performing HRC analysis, Huvanandana et al et al indicated that this drug not only affects and increases the HR and beat-to-beat pulse pressure variability but also has a definite effect on blood pressure (22).

The present research reviewed the HRC of an infant who received caffeine in the NICU of Akbar Abadi hospital in Tehran. According to the diagrams, the infant's HR increased, which was observable in HRC. Three factors were examined to analyze the ECG signal. Figure 4 shows a noticeable decrease in the RR interval, which is essential since this decrement is consistent with the previous observations, indicating irregularities and regularities in the RR interval before and after administration, respectively. Figure 5 shows that the distribution of the RR interval becomes abnormal and the average point changes after caffeine administration, representing the apparent effect of the drug. Further, the sample asymmetry number was the essential factor that profoundly changed in HR after drug administration. This change was more pronounced compared to other changes in HRC.

As mentioned earlier and according to the definition, irregularity in the signal characteristic (i.e., the RR interval and beat number) indicates the infant's health given that the irregularity has a normal distribution. Deviations from a normal distribution (deceleration) indicate sepsis. This study evaluated the statistical distribution of the RR interval time and found that this distribution can be beneficial for prognosis. However, as an innovation, it requires further evidence since the observation of significant changes in this characteristic can help us to identify the factor with a more significant correlation with the drug effect.

Given the importance of diagnosis and prediction of sepsis, which is responsible for the mortality of many premature infants, and according to the reviewed studies in this article, one can claim that the drug effect on HRC can result in an error in the engineering diagnosis of sepsis in premature infants.

Limitations

In this study, the researcher had to use three cardiac leads to obtain ECG data, and premature infants were extremely small, thus it was very difficult for the leads to stick properly on their chests. Nurses should visit their infants regularly during the study to make sure the infant's test lead is well connected. On the other hand, since newborns' skin is highly sensitive, care should be taken not to damage their skin as a result of the repeated use of this kind of chest leads and keep the data well connected during clinical examinations. Besides, due to the conditions and facilities of the hospital, it was necessary for the infants to be transferred to other incubator beds, and it happened many times. Therefore, we had to be careful about recording one person in the central data system, otherwise, the data would be unusable. Due to the high stress of nurses in the NICU, the study of this project with these restrictions put double stress on them, which could cause data collection errors or endanger the health of infants. Accordingly, subspecialist colleagues and nurses made huge efforts for proper evaluations during this project. However, the above-mentioned limitations occasionally led to errors in data collection. Another problem was the speed and accuracy of ECG data acquisition with a data sampling rate of 200 samples/second, which can be used in subsequent experiments with devices with a higher sampling rate.

Furthermore, it is suggested that future researchers, by the evaluation of more groups of premature infants and their HRC analysis and considering significant changes observed in this study, develop a mathematical model of this drug or obtain similar characteristics such as the HeRO score to be able to develop and generalize the engineering prognosis. The effect of other drugs on the infant's heart can be examined as well. Accordingly, more accurate predictions can be made by strengthening artificial intelligence and providing different models of HRC changes from any type of drug and collecting data from the whole world. This research could be a good start for an extensive study of modeling the effects of drugs on HRC. Various analyzes, especially in the time-frequency domain (e.g., wavelet analysis methods) can greatly contribute to the efficiency of these analyzes. Finally, the study could also evaluate changes in the HRC of the heart in adults and look beyond the scope of premature infants.

Conclusions

In general, this study examined the effect of caffeine administration on an infant's ECG signal in the NICU. To this end, 20 premature infants were tested in this study. Of these infants, 15 cases received caffeine among whom, there were babies who dropped out due to two or more illnesses or medication. HRC changes in the premature infant before and after caffeine injection and its analysis help us to pay more attention to the confounding factor in new types of disease prognosis methods. Moreover, these changes can affect the prediction process performed according to ECG signals, including the HeRO score, which is used to predict infections in newborns. This score uses the HRC analysis, similar to this study, to detect prognosis before the onset of clinical symptoms in newborns. Therefore, it is essential to investigate the effect of a drug (e.g., caffeine which is highly prescribed for children in NICUs) on HRC in order to develop and generalize engineering prognosis for the prediction of lethal deaths in preterm infants through vital signals.

In this study, there was a noticeable change in the heart signal skewness and a change in RR interval distribution. Thus, further research and evidence can help mathematical modeling and development of advanced prognostic devices for the prediction of infection by considering drug effects in their calculations and smartly identifying the effects of this drug or similar drugs that can affect the heart and its characteristics after administration.

It should be noted that the studied premature infant had no proven sepsis in this valuable research, and we only investigated the effect of caffeine in the HRC analysis. Besides, the elimination of noise or outliers is of particular importance in the prognosis phenomenon. If more factors are taken into account, the prognosis accuracy can be increased while reducing the confounding effects of the drug.

Conflict of Interests

The authors declare that they have no conflict of interests.

Ethical Issues

The ethical code for this research is IR.TUMS.CHMC.REC.1398.039. The project was found to be under the ethical principles and the national norms and standards for conducting medical research in Iran.

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