Newborn infant pain assessment using heart rate variability analysis.

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Financial support :

The study was supported in part by a grant from the French National Research Agency (ANR-07-PEMBP-00X).

Abstract

Objectives: Systems controlling cardiovascular function are closely coupled to perception of pain. Heart rate variability (HRV) is a well-established non-invasive measure of cardiac autonomic control. We hypothesized that pain may alter HRV in the newborn infant and that HRV analysis could be used as an indicator of prolonged pain in the newborn infant.

Methods: To test the hypothesis, we measured the magnitude of the heart rate high frequency variations using an innovative High Frequency Variability Index (HFVI) in newborn infants at risk of postoperative pain. We investigated newborn infants with a gestational age (GA) > 34 weeks and who were admitted after a major surgical procedure. Inclusions were performed from 2 to 72 hours after the surgery. The postoperative pain was scored using EDIN scale (neonatal pain and discomfort scale) at the end of the 2 hours recording period. The infants were separated in: 1) Group "Low EDIN", when EDIN<5; and 2) Group "High EDIN", when EDIN≥5. Predictive positive and negative values of a threshold value of HFVI in assessing pain have been studied.

Results: 28 newborn infants were enrolled in the study (mean GA=37.8±1.5 weeks) at a median delay between the surgery and the recording of 5 hours. Mean EDIN were 2±1 and 7±2 in respectively the groups "Low EDIN" and "High EDIN". The 2 groups were similar for GA, basal heart and respiratory rates, SpO_2, mean arterial blood pressure, and morphine infusion rate. HFVI was significantly lower in the group "High EDIN" than in the group "Low EDIN" (0.7±0.2 versus 1.2±0.3 respectively; $p<0.01$). An HFVI < 0.9 was able to predict an EDIN score ≥ 5, with a sensitivity of 90%, and a specificity of 75%.

Discussion: This study indicates that postoperative pain is associated with a decreased high frequency HRV in full-term newborn infants. Our findings suggest that heart rate variability could be used as an indicator to assess prolonged pain in the newborn infants.

Key words: newborn, pain assessment, autonomic nervous system, heart rate variability

INTRODUCTION

Concerns about short- and long-term adverse consequences of early pain exposure in newborn infants imply to develop valid and reliable measures of infant pain. Indeed, the plasticity of developing brain is vulnerable to stress, that in turn may cause long term neurodevelopmental changes, including altered pain sensitivity and neuroanatomic and behavioural abnormalities (1,2,3).

During neonatal intensive care stay, large number of painful procedures are performed, the majority of which are not accompanied by adequate analgesia (4,5). Optimal management requires competent pain assessment which can be especially difficult to perform in this non verbal population. Various pain assessment scales has been developed, mainly based on both behavioural and physiological indicators of pain. These scoring systems allow bedside evaluation and help decision taking for managing pain. However, they have some limitations: 1) reliability has been questioned even when performed by well-trained nurses, in particular in distinguishing pain and discomfort; 2) some pain scales require prolonged clinical observation of the infants, especially for assessing prolonged pain; and 3) pain scoring is intermittent, with a risk to not take into account some painful episodes during the inter-rating period. So, there is a need for further investigations to assess pain in the newborn infant.

Previous studies clearly showed that systems controlling cardiovascular functions are closely coupled to systems associated with perception of pain (6,7). Many brain regions receive convergent nociceptive inputs and contain groups of neurons that initiate autonomic responses to these stimuli. Extensive interactions exist between the nociceptive and the autonomic systems at the levels of the central and peripheral nervous systems (7). Heart Rate Variability (HRV) is a well-established non-invasive measure of cardiac autonomic control (6, 8). HRV is mediated primarily by changing levels of parasympathetic and sympathetic

outflow from the central nervous system to the sinoatrial node of the heart. Studies using selective pharmacological blockade of the cardiac sympathetic and parasympathetic receptors have shown that fluctuations in heart rate (HR) above 0.15 Hz and centered at the respiratory frequency, are mediated exclusively by changes in parasympathetic outflow, whereas lower frequency changes are mediated by both changes in parasympathetic and sympathetic outflows (9,10). In adult, growing evidence highlight that pain, fear or anxiety result in decrease in the HRV, in particular the high frequency (HF) power (> 0.15Hz), indicating a drop in vagal tone during unpleasant stimuli or emotion (11,12,13). During surgical procedure in adult patients, HRV is correlated with the balance between the nociceptive stimulus and the level of analgesia (14). In infants, a decreased spectral power in the high frequency band has been observed during routine heel lancing procedure, suggesting a decrease in parasympathetic output during acute nociceptive stimuli (6,15). To the best of our knowledge, the specific autonomic control mechanisms that underline cardiac response to painful stimuli in the newborn infant are not known.

We hypothesized that noxious events may alter HRV in the newborn infant and that could be used as an indicator of prolonged pain in the newborn infant. To test the hypothesis, we measured the magnitude of the HF variations in HRV in newborn infants at risk of postoperative pain. HRV was analyzed using a new validated algorithm, which allows accurate assessment of rapid changes in autonomic nervous system outflow (16). The postoperative pain was scored by using EDIN scale (neonatal pain and discomfort scale) validated for assessing prolonged pain at bedside in the newborn infant (17). EDIN scale has been validated for assessing prolonged pain in term and preterm newborn infants (17, 18). Predictive positive and negative values of a threshold value of HFVI in assessing pain have been studied.

MATERIALS AND METHODS

Population:

We investigated newborn infants with a gestational age above 34 weeks and who were admitted after a major surgical procedure in the neonatal intensive unit at the Lille University Hospital (level III nursery) between 01/2008 and 12/2008. Inclusion in the study was performed from 2 to 72 hours after the surgery, starting after respiratory and hemodynamic stabilization. Exclusions criteria were: 1) circulatory failure requiring infusion of vasopressive drugs or fluid resuscitation; 2) severe respiratory failure requiring high frequency oscillatory ventilation and/or O_2 need > 35%; 3) infants with congenital or acquired neurological abnormalities; and 4) infants with cardiac malformation or arrhythmias.

Post-operative analgesia was performed using continuous infusion of morphine. Rate of drug infusion was adjusted according to the EDIN pain scale score. The EDIN scale is a unidimensional scale using 5 behavioral indicators: facial activity, body movements, quality of sleep, quality of contact with nurses, and consolability (17). Each indicator is scored from 0 to 3. EDIN scale is the sum of the 5 items and ranges from 0 to 15. EDIN score at a given time point has been specifically developed for assessing the mean wellbeing or pain during the preceding hours (17). It has been used in preterm and full-term newborn infants, in particular to assess post-operative pain (17, 18). Inter-rater reliability as well as internal consistency were found acceptable (17). However, in our experience, accurate assessment requires extensive experience with neonates to evaluate consolability and sociability. Prolonged observation of the infants is also required to determine their responses to stimulations. Thus, the nurses involved in this study, had specific training in pain assessment and in using the EDIN scale. As some indicators of the scale, such as quality of contact or consolability, may require prolonged relation with the infant for accurate assessment, the

EDIN scores were measured by the nurse in charge of the infant after at least 2 hours of observation. The rate of morphine infusion was increased when EDIN score was ≥5.

This non-interventional and observational study was approved by the local Institutional Review Board. The parents were informed of the study protocol and of the management of pain control protocol in our NICU.

Study design

After inclusion in the study, physiologic parameters were recorded every 30 minutes for 2 hours: heart and respiratory rate (HR and RR), O_2 need, transcutaneous arterial oxygen saturation (SpO_2), transcutaneous $PaCO_2$ ($TcPCO_2$), mean arterial blood pressure (MAP), and cutaneous temperature. The analogical output of the monitor (Merlin, Philips, Netherlands) was connected to a personal computer for real time acquisition of the electrocardiogram (ECG) using a data acquisition board (Physiotrace®, Estaris Monitoring, France; CE marked for clinical use). ECG was stored on the computer for later HRV analysis. The infant was observed by the nurse during the 2 hours of the study period. Special care was taken to prevent from stimulation of the infant and to control the environmemental conditions (low light and noise) during the study period. EDIN was scored at the end of the recording period. Morphine infusion rate was not changed during the study period. The infants were separated in 2 groups: 1) Group "Low EDIN", when EDIN score was lower than 5; 2) Group "High EDIN", when EDIN score was equal or above 5. This cut off value was chosen because our local guidelines for pain management include use of analgesic when EDIN score ≥5.

HR variability analysis

HRV analysis was based on a time analysis of HR in the high frequency domain.

RR series acquisition:

ECG signal was digitized at a sampling rate of 250 Hz. The time interval between two R waves of the ECG (RR value) was measured using an R wave detection algorithm (19). The

accuracy of the instantaneous RR values was 4ms. RR intervals series was filtered in real time using an effective filtering algorithm preventing from artefacts-induced inaccurate measurement of RR intervals series (20) and re-sampled at 8 Hz using a linear interpolation algorithm (14,16,19,20).

RR samples windowing, normalizing and filtering:

The RR samples were isolated into a 64 seconds moving window (512 samples) for RR series analysis. For reliable inter patients comparability, the signal was normalized within the moving window using the following algorithm. In a first step, the mean value (M) was computed as: $M = \frac{1}{N}\sum_{i=1}^{N}(RR_i)$, where RR_i represents the RR samples values and N the number of samples in the window. Then M was subtracted from each sample of the window as: $RR_i = (RR_i - M)$. The norm values (S) were then computed as: $S = \sqrt{\sum_{i=1}^{N}(RR_i)^2}$. Each resulting RR sample was divided by the norm value S: $RR_i = RR_i / S$

To analyse the high frequency variations, RR samples were band pass filtered from 0.15 Hz to 2 Hz using a wavelet based numerical filter providing RRhf (14,16,19). The High Frequency Variability Index (HFVI) was computed as the area under the curve inside the 64 seconds window: $HFVI = \frac{1}{fe}\sum_{i=1}^{N}|RRhf_i|$, where $RRhf_i$ represents the RRhf samples values, N the number of samples in the window and fe the sampling frequency.

Statistical analysis

Data were analyzed with a personal computer-based statistics package (SPSS for Windows). Standard linear regression analysis was used for comparison of EDIN score expressed as a continuous variable with the mean value of the high frequency variability index (HFVI). Sensitivity and specificity were computed for HFVI to determine which level best predicted EDIN score ≥ 5. A EDIN score ≥ 5 was considered as related to significant pain or

discomfort. Receiver Operating Characteristic (ROC) curves were obtained by using EDIN scores ≥ 5 as actual state variable and HFVI as test result variables. Area under the ROC curves and best cutoff values for HFVI were calculated. Mann-Whitney test (independent values) and paired Wilcoxon rank test (paired values) were used for the comparison of groups. The physiological parameters were expressed as means ± standard deviation (SD). P value of <0.05 was considered significant.

RESULTS

Twenty eight newborn infants were enrolled in the study (13 girls). All the infants were admitted in the NICU just after birth. The mean gestational age was 37.8±1.5 weeks (8 preterm infants, 35 and 36 weeks GA), and the mean postconceptional age at the inclusion was 39.6±1.2 weeks. Mean weight at the inclusion was 3300±350 g. The infants were exposed to various noxious stimuli before the surgical procedure, such as heel pricks, tracheal suctioning, orogastric tube insertion. The median delay between the surgical procedure and the recording was 5 hours (range 2 to 18 hours). The indications of the surgery were: intestinal obstruction (5), necrotizing enterocolitis (6), oesophageal atresia (7), gastroschisis (2), sacrococcygeal teratoma (2), congenital diaphragmatic hernia (2), cystic adenomatoid malformation (2), nasal glioma (2). All the infants underwent a major surgical procedure including thoracotomy and laparotomy, at high risk for post-operative pain experience.

Table 1 shows the characteristics of populations in the two groups. Mean EDIN were 2±1 and 7±2 in respectively the group “Low EDIN” (n=10) and the group “High EDIN” (n=18). All the infants were mechanically ventilated except 2 infants in group “Low EDIN” and 1 infant in group “High EDIN” (nasal ventilation). The 2 groups were similar for GA, postconceptional age at inclusion, weight, and delay between surgery and the recordings (Table 1). Morphine infusion rate did not differ between the 2 groups. Heart and respiratory rates, SpO_2 (transcutaneous oxygen saturation), $TcPCO_2$ (transcutaneous partial pressure of

CO_2), mean arterial blood pressure, and O_2 need were not significantly different between the groups (Table 1).

Despite similar basal mean heart rate, HFVI was significantly lower in the group "High EDIN" than in the group "Low EDIN" (0.7±0.2 versus1.2±0.3 respectively; $p<0.01$) (Fig 1). The difference in HRV can be graphically appreciated in Fig 2 showing individual tracings of RR series after normalization and filtering in an infant with low EDIN score and an infant with high EDIN score.

The HFVI was significantly correlated to EDIN score ($r=0.7$; $p<0.01$) (Fig 3). An HFVI of 0.9 was found to be the optimal cut off point to predict an EDIN score ≥ 5, with a sensitivity of 90%, and a specificity of 75%. The area under the ROC curve was 0.81.

DISCUSSION

In neonatal intensive care unit, management of pain remains challenging because no gold standard exists for expression and assessment of neonatal pain. HRV is controlled by the autonomic nervous system, which is modulated by noxious events. We studied HRV in newborn infants at risk of postoperative pain. We found that HRV is decreased in the newborn infants with an EDIN score ≥ 5, indicating a decreased parasympathetic outflow in painful newborn infants. A high frequency variability index lower than 0.9 predict an EDIN score ≥ 5 with a sensitivity of 90% and a specificity of 75%. Taken together, these data suggest that heart rate variability could be used as an indicator to assess pain in the newborn infants.

Relation between HRV in the HF band and stressful or painful conditions has been largely studied in adults (14). Patients with uncomplicated painful angina had reduced HRV affecting mainly the high frequency band (21). A marked decrease in the high frequency HRV is seen during painful events, such as surgical procedure (14,19). Stressful event and anxiety induce a drop in the high frequency HRV (11, 22, 23). Few studies exist in the neonates. Elevation in

HRV has been observed during Kangaroos care in the newborn infant, likely through reduction in stress (24,25). In preterm infants, observation of facial signs of pain has been associated with decreased HRV (26). In 4- and 8- month old infants, acute nociceptive stimuli such as heel prick procedure, lower HRV (6, 15). Our study provides additional information regarding the effect of prolonged pain on HRV in the newborn infant. We found that high frequency HRV was higher in the infants with low EDIN scores compared to the infants with elevated EDIN scores. EDIN is a validated neonatal pain scale that provides reliable assessment of pain intensity in neonates (17). Many factors have the ability to alter HRV, such as maturation of the autonomic nervous system (27), hypoxia, hypercapnia and acidosis (28), basal heart rate (29), arterial blood pressure (30), or various drugs such as opioids or hypnotics (14,31). Both opioids and hypnotics decrease the overall heart rate variability but increase the high- to low-frequency components ratio (14,31). In adult patients, nociceptive stimuli during surgery decrease HRV in the HF band in condition of light analgesia (inadequate) (14). Environmental conditions such as light and noise may also alter HRV (29). At the opposite, HVR is similar in mechanical or spontaneous ventilation (32). In our study, the difference in HRV between the infants with low and high EDIN scores was not related to developmental differences as both gestational and post-conceptional ages were similar in the 2 groups. In the same way, blood gas parameters, basal heart rate and pressure, and morphine infusion rate were similar in the infants with low and high EDIN scores. None of the included infants received hypnotic or sedative drugs. Furthermore, the environmental conditions were tightly controlled and similar for each included infant in the present study. Thus, our data provide additional evidence that pain reduces HRV in the HF band in the newborn infant.

Analysis of HRV is widely used as a tool to assess autonomic nervous system activity in many clinical conditions, including assessment of anaesthesia depth (14), affective disorders (11, 12, 33). In the fetus, a relative decrease in HRV greater than 30% predicts cord arterial

metabolic acidosis with a high sensitivity and specificity (34). HRV is decreased by the pain, and was found to be a reliable marker of pain sensitivity in adult (13).Our study highlights that HRV analysis can also be used as a clinical tool to assess pain in the newborn infant. A low HRV in the HF band is able to identify prolonged pain with a good sensitivity and specificity in newborn infants at risk of postoperative pain. Although many scales exist for evaluating procedure related acute pain and treatment efficacy in neonates, very few tools are available for assessing prolonged pain -i.e. lasting several hours or days- in the neonate. Yet many conditions common in newborns may cause prolonged pain such as abdominal distension, nasal lesions during CPAP, or postoperative period. EDIN pain scale is based on 5 behavioral indicators specifically chosen to assess prolonged pain in the newborn infant. Reliable EDIN scoring requires prolonged observation -at least for one hour- by well-trained nurses. In clinical setting, EDIN is scored once or twice a day. Thus, fluctuation of pain intensity can go unrecognized and therefore untreated. A consensus has been reached that appropriate pain management is a key priority in neonatal care (35). Pain assessment is a prerequisite to gauge analgesic needs and to evaluate the efficacy of analgesics. We propose that HRV analysis can be used as an additional tool to detect potential painful newborn infants in high risk conditions. HRV analysis is easy to perform, can be continuously monitored, and is noninvasive. Low HRV in the HF band may alert that an infant is potentially painful, and should prompt the nursing staff for clinical pain scale scoring.

Our study has some limitations. First, HRV is controlled by the autonomic nervous system outflow, which is altered by numerous factors including maturation, environmental conditions or drugs. Our studied population was highly selected and enrolled full-term newborn infants after a major surgical procedure. All the infants were treated by morphine. The environmental conditions were tightly controlled. Whether or not our findings may apply in other populations of neonates remains an open question. Second, in this study, HRV was not

assessed prior the surgery. Thus, we cannot exclude that basal HRV in the "high EDIN" group could have been lower than in the "low EDIN" group. Future studies should include longitudinal assessment of HRV to strengthen our results.

CONCLUSION

This study indicates that postoperative pain is associated with a decreased high frequency HRV in full-term newborn infants. Low HRV identifies with a good sensitivity infants with significant prolonged pain. Further clinical studies comparing newborn infants who underwent surgical procedure and controls are required to assess whether HRV can be used as an indicator to assess prolonged pain in the newborn infants. Compared to acute pain, prolonged pain may be largely unrecognized in the newborn infants -and therefore untreated-. Many conditions exist in NICU during which newborn infants may experienced prolonged pain. Examples include mechanical ventilation, nasal lesions during nasal continuous positive airway pressure, abdominal distension, necrotizing enterocolitis or pain after a surgical procedure. Although prolonged pain can be assessed by using validated scales in the newborn, it may be underestimated because pain scoring is performed usually twice or 3 times a day in clinical setting. Development of new tools to assess pain in the newborn infant is therefore required. Quantitative and continuous assessment of HRV analysis can be obtained from usual electrocardiographic monitoring, on condition that effective filtering algorithm prevents from artefacts-induced inaccurate measurement of RR intervals series (20). We propose that a decreased HRV, especially in the high frequency band, might help to identify potentially painful infants, and could be used as an alert signal to prompt the nursing staff for clinical pain scale scoring.

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Legends

Fig 1: Heart Rate Variability in the high frequency band (Mean HFVI) in group "Low EDIN" (EDIN score < 5) and in group "High EDIN" (EDIN score ≥ 5). Mean HFVI is significantly higher in the group "Low EDIN" than in the group "High EDIN" ($p<0.01$). A high EDIN score ≥ 5 is usually considered as indicative of prolonged pain in the newborn infant.

Fig 2: Individual tracings of RR series (after band pass filtering of the RR samples from 0.15 Hz to 2 Hz) in 2 full-term newborn infants during postoperative period. Panel A: infant with mean EDIN score = 2 (considered as indicative of minimal pain). Panel B: Infant with mean EDIN score = 7 (considered as indicative of significant pain). Compared to panel A, variability of RR series (mainly modulated by respiratory rate) is decreased in Panel B.

Fig 3: Correlation between Heart Rate Variability in the high frequency band (HFVI) and EDIN scores. HFVI is inversely correlated with EDIN score ($r=0.7$, $p<0.0001$). EDIN score increases with pain intensity in the neonates.

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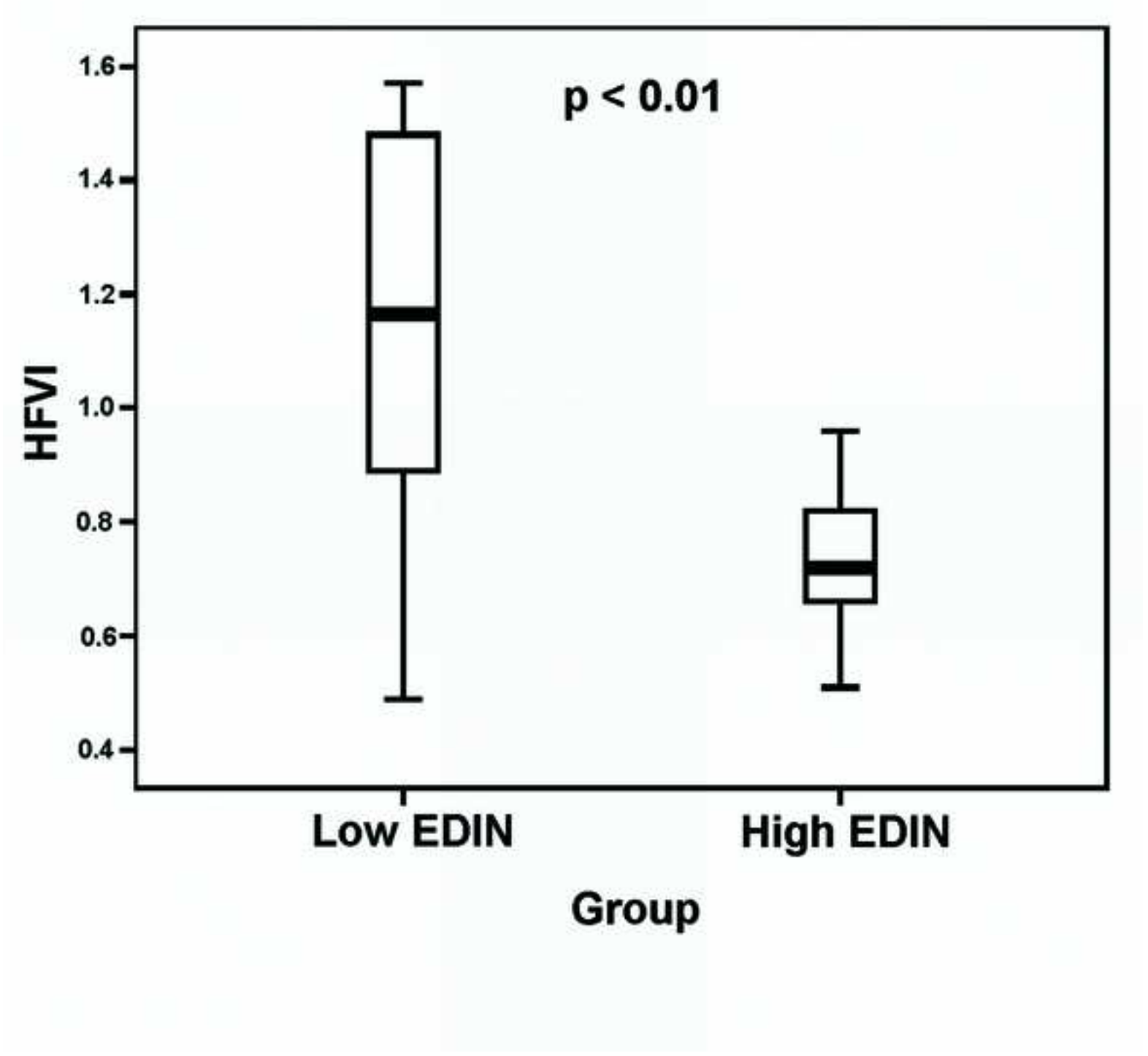

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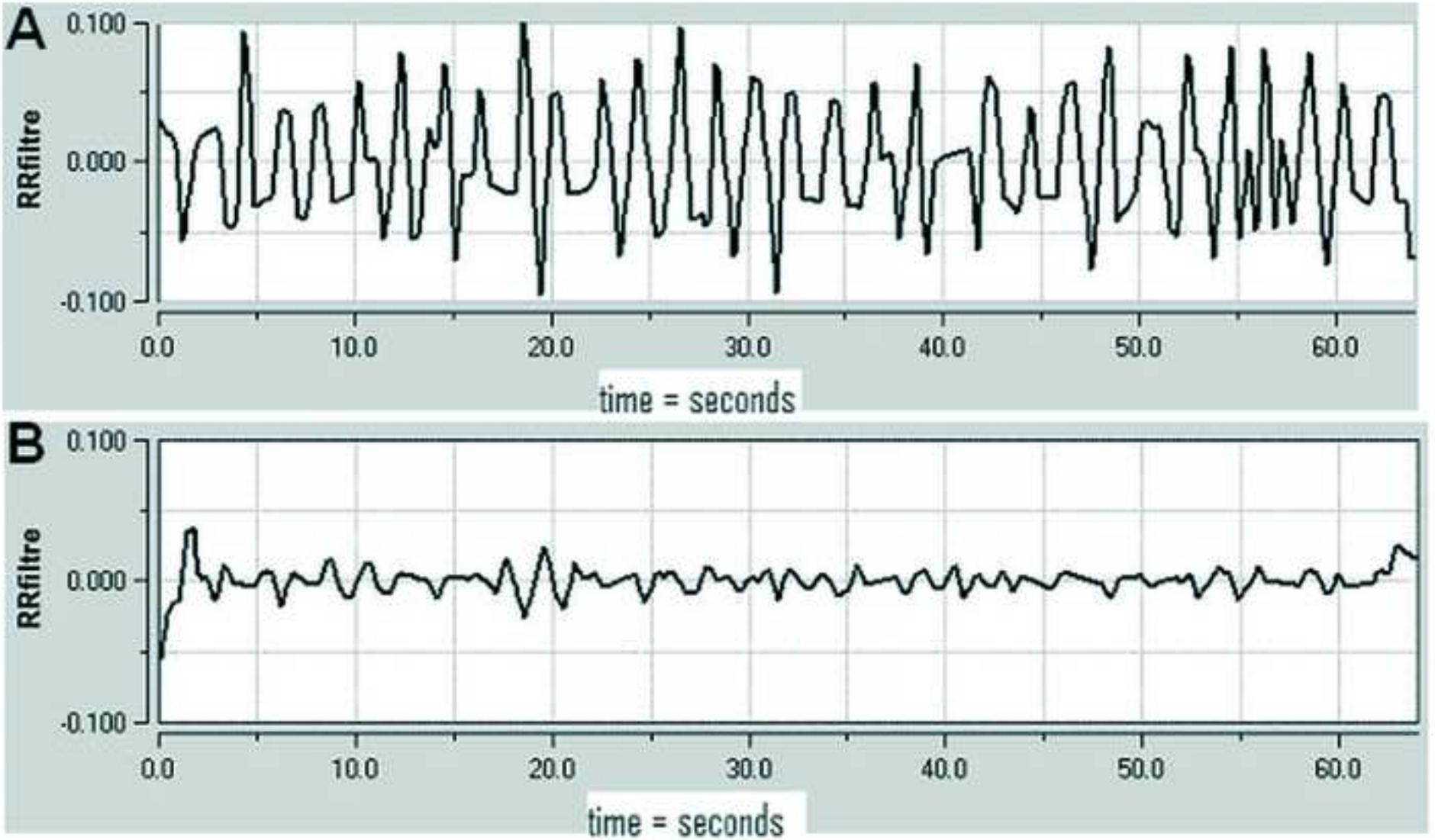

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