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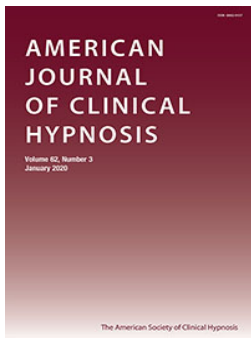
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Autonomic Cardiac Reactivity to Painful Procedures Under Hypnosis in Pediatric Emergencies: A Feasibility Study

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Pain sensation is characterized by abrupt changes in central nervous system activity producing autonomic reactivity. While clinical hypnosis has demonstrated its benefits for children in pain management, it is not clear whether hypnosis modulated autonomic pain response in children in clinical conditions. Here, we studied autonomic responses under hypnosis to sutures in pediatric emergencies. For that, 42 children (mean age: 6.5 years, range 1.5 to 13) were divided into two groups consecutively (hypnosis and control groups), according to their choice. Time-frequency analysis was applied on RR intervals (heart rate interbeat intervals, or RRI) to estimate parasympathetic reactivity based on high frequency power (HF) and the Analgesia Nociception Index (ANI®) and on sympathetic reactivity (low frequency power [LF]) and LF/HF ratio). We observed that RRI and LF/HF ratio varied according to suture and hypnosis ($p < 0.05$): RRI was higher and LF/HF ratio was lower during sutures in the hypnosis group in comparison to the control group whereas HF and ANI® increased only during hypnosis. To conclude, hypnosis in pediatric emergencies reduces sympathetic cardiac pain reactivity and could be a marker of pain relief under hypnosis, while parasympathetic activity seems to be a better marker of hypnosis.

Keywords: Pain, Suture, Autonomic nervous system, RRI variability, Analgesia and Nociception Index®

The assessment of pain in pediatric emergencies is a priority for efficient pain management. However, pain is a private experience, accessible to others only through verbal reports. When children are able to communicate their own pain to a physician, self-rating scales such as the Visual Analog Scale (VAS) allow good pain assessment (Bailey, Gravel, & Daoust, 2012). However, when these patients cannot easily communicate their perception, their management is difficult. A Canadian study in 2008 (Taylor, Boyer, & Campbell, 2008) found that 77% of hospitalized children felt pain during hospitalization and only 58% had received analgesic treatments. To resolve this problem,

development of pain markers may allow monitoring and relief of pain in these children. Studying cardiac reactivity is one of the potential methods to approach pain in children who cannot easily communicate their pain (Chouchou et al., 2011; Wodey et al., 2003).

Among the different methods of studying this cardiac autonomic reactivity, two methods are used: RR intervals (heart rate interbeat intervals, or RRI) variability and the Analgesia Nociception Index® (ANI®). Evaluating RRI variability (or heart rate variability) is a common noninvasive method for assessing sympathetic and parasympathetic activities. The power of high frequency (HF) variations of the RRI is considered to be a marker of parasympathetic control, while that of low frequency (LF) RRI variations and the ratio of low-to-high-frequency powers of RRI variations (LF/HF ratio) are markers of sympatho-vagal balance (Malliani, Pagani, Lombardi, & Cerutti, 1991). The ANI® is based on the variations of the normalized HF units and is developed to study parasympathetic modulations in reaction to pain (Avez-Couturier et al., 2016).

Hypnosis offers a valuable approach to improve pain management in pediatric emergencies (Lioffi & Hatira, 1999; Thibault-Wanquet, Penhoet, & Moreaux, 2009; Wood & Ignace, 2007). The effectiveness of hypnosis to decrease pain and anxiety has been demonstrated (Faymonville et al., 2000a; Vanhauzenhuysse et al., 2009), leading to significant reduction in drug requirements and improving the comfort of these young patients.

In this vein, the development of pain markers would be an important step to monitor hypnosis (Diamond, Davis, & Howe, 2008) and its effect on painful perception and to improve the well-being of patients. Thus, the aim of this study was to assess cardiac reactivity to a suture using RRI and ANI® in monitoring of pain sensation in pediatric emergencies with or without hypnosis. We studied the feasibility of this type of approach to monitor pediatric emergency pain with and without hypnosis. According to previous studies (Aubert, Verheyden, Beckers, Tack, & Vandenberghe, 2009; Chouchou et al., 2011; DeBenedittis, Cigada, Bianchi, Signorini, & Cerutti, 1994; Diamond et al., 2008; Fauchon et al., 2018; Hippel, Hole, & Kaschka, 2001), we hypothesized the following: (1) the sutures should induce a sympathetic cardiac response in each group and (2) the hypnosis group should have a lower sympathetic response because hypnosis is known to reduce pain perception.

Methods

Participants

Forty-two patients (16 females and 26 males, age 6.5 ± 2.7 years (standard deviation, range 1.5 to 13) completed the study. Subjects were recruited in the pediatric emergency unit of the University Hospital of Saint-Etienne. Patients with one or more superficial sutures were included without known cardiovascular diseases (such as arrhythmias) or any disability that prevents the understanding of instructions. We proposed the study to

all patients and their parents, suffering from a superficial wound requiring one or more stitches, without mental retardation and without known cardiovascular pathology. Among the patients to whom we proposed the study, all were included, except one. This patient was not included in the study because his parents did not give their consent due to an inability to understand French. Indeed, as they did not speak French, they could not understand the study. The study was approved by the ethics committee of the Saint-Etienne Hospital (IRBN342016/CHUSTE) and was in agreement with the Declaration of Helsinki. All patients and their parents gave their consent.

Experimental protocol

After admission in pediatric emergency, 22 patients took oral paracetamol and the wound was cleaned and anesthetized with local Xylocaine® for all patients. For optimal drug efficiency, surgical procedures started 20 min after drug intake. Children were included into two different groups according to the child's choice: (1) the hypnosis group ($n = 21$) receiving nitrous oxide (an equimolar mixture of oxygen and nitrous oxide) and hypnosis by qualified nurses or physicians or (2) the control group ($n = 21$) receiving nitrous oxide only (Brown, Hart, Chastain, Schneeweiss, & McGrath, 2009).

Hypnosis is used in pediatric emergency care by qualified nurses or physicians with the aims of improving the well-being of the patient and helping the patient to ignore the hospital environment and the suture. Hypnosis began simultaneously with the nitrous oxide, one minute before the suture. The nitrous oxide contains 50% oxygen and 50% nitrous oxide (Goerig & Schulte Am Esch, 2001). The oxygen facilitates breathing and prevents potential bradypnea provoked by the nitrous oxide.

Physiological recordings began one minute before the suture and was stopped one minute after the suture to allow for pre- and post-suture reference periods. The suture duration was very heterogeneous. It could be five minutes or 45 minutes, depending on the interactions between patients and physicians or nurses and the amount of suturing required. The patient could leave the hospital when the treatment procedures were finished and after a few minutes of rest, according to medical advice.

Hypnotic induction

We applied different steps in the induction of hypnosis (Barabasz & Barabasz, 2016), as follows: first, the nurse (hypnotherapist) talked to the patients about their hobbies, school, and home life to better know them and to hold their attention during the surgical material preparation. Then the hypnotherapist induced the hypnotic trance by asking the patient to close his or her eyes, to gradually focus on physical, visual, and auditory sensations, and to breathe deeply. Then, the nurse whispered a story to the

child based on his or her memories and sensations, while the child kept the eyes closed. During the hypnotic trance, the previously elicited memories and sensations were recited to the subject along with suggestions of physical well-being while the medical intervention (5–10 min) was carried out. The patients confirmed their comfort by raising a finger. At the end of the clinical intervention, the nurse then gradually brought the subject back to normal consciousness.

Electrophysiological recordings

Three electrodes were used to record (ECG) with an MP20® device (Phillips, Netherlands). These electrodes were placed on the chest of the patient. The acquisition was made at 256 Hz. The channel presenting the best signal/noise ratio was conserved for further analyses. The ANI® was recorded with an ANI® monitor (MDoloris Medical System®, France) connected to the electrocardiogram monitor.

The physiological signals were recorded with a multifunction data acquisition unit (USB-6000®, National Instruments Inc., USA) and stored in a laptop (Atitude®, E5500, Dell, USA) using an acquisition software developed under Matlab® R2015b software (MathWorks, USA). The time of sutures was manually introduced in the recordings with an event marker included in the software.

Data analysis

Heart rate variability analysis

To study autonomic cardiac activity, a continuous beat-to-beat analysis of the ECG was applied to detect the R peaks of the QRS complex with a free software (Pichot, Roche, Celle, Barthélémy, & Chouchou, 2016). First, RRI were automatically extracted from the ECG signal. Manual correction of artifacts, ectopic beats, or undetected normal R peaks was applied. Afterward, R peaks not manually corrected (artifacts, ectopic beats, etc.) were interpolated (Pichot et al., 2016). RRIs were studied 10 RRIs before and 30 RRIs after the suture (Chouchou et al., 2011).

Time-frequency analysis of the RRI signal was used, using the wavelets transformed with a mother wavelet “Daubechie,” which can, by dilatation and translocation along the signal, decompose it into its different frequencies and then extract the sympathetic and parasympathetic components and their modulation as a function of time (Pichot et al., 1999, 2016).

HF power (0.15–0.40 Hz) is related to the parasympathetic activity and LF power (0.04–0.15 Hz) to parasympathetic and sympathetic activities. An increase in the LF/HF ratio in response to a noxious stimulation reflects the prevalence of the sympathetic system on the parasympathetic one (Malliani et al., 1991). RRI variability indices were studied 10 s before and 30 s after the suture.

Analgesia and Nociception Index Analysis

To complete the study of parasympathetic reactivity to pain and hypnosis, we analyzed Instantaneous and mean ANI® indices. The instantaneous ANI® index, based on HF power of RRI variability, is given every second and the mean ANI® index is the mean of the ANI® values during the prior minute. This index is given on a scale of 0 to 100. At 100, the patient is considered to not be experiencing pain, and when this index reaches 70 on the scale, the patient is considered to be in pain (Jeanne, Clément, De Jonckheere, Logier, & Tavernier, 2012). ANI® indices were studied 10 s before and 30 s after the suture.

Statistical analysis

Data analyses were performed with Statview (SAS Institute Inc®, USA). We computed the mean RRI, HF^{WV} , LF^{WV} , LF^{WV}/HF^{WV} , and ANI®. The mean of absolute values per each experimental condition were studied to understand overall autonomic activity during hypnosis. Secondly, to study autonomic reactivity to suture and its interaction with hypnosis, we used normalized induces. Data were normalized by calculating the percentage of change during each experimental condition relative to their respective baseline (% change = $100 * \text{parameter value}/\text{baseline average}$). Baseline from 10 s to 1 s before sutures was used.

The absolute values of each group were submitted to the following: (1) a nonparametric Mann-Whitney test to compare the two groups (hypnosis group and control group) and (2) normalized values to a repeated measures analysis of variance (RM-ANOVA) with two factors: the time (pre- vs. post-suture) and the experimental condition (hypnosis vs. control groups). Analyses were made between the mean of 10 s before the suture and and of a period of 5 seconds after the suture corresponding to the maximum change after the suture. Differences were considered significant when the *p* value was less than 0.05 and values are expressed as mean \pm SEM.

Results

Feasibility and clinical description of the population

Forty-two patients participated in the study; they were divided into two equal groups: (1) The control group, age 5.7 ± 2.2 years and composed of 11 females and 10 males with a mean of 3.6 ± 1.9 suture points, and (2) the hypnosis group, age 7.1 ± 3.0 years and composed of 5 females and 16 males with a mean of 3 ± 1.6 sutures. All patients received nitrous oxide, and 11 in each group received paracetamol.

Sutures were made at different parts of the patients' bodies: mainly on the forehead ($n = 5$) for the control group and on the chin ($n = 6$) for the hypnosis group. There were also suture points on temples, fingers, back, knees, eyebrow arches, and lips.

During recordings, the ANI® monitoring failed to detect some heartbeats. We had to exclude six patients in the hypnosis and 7 in control groups for the ANI® analysis due to loss of signal. For ANI®, statistical analyses were applied to 15 patients in the hypnosis group and 14 in the control group. In the same way for the RRI analysis because of artifacts, we eliminated four patients in the hypnosis group and 1 for the control group. Thus, RRI analysis was applied to 17 in the hypnosis and 20 in the control group. Overall, from a feasibility point of view, 31.0% of ANI® recordings were not usable and only 11.9% of ECG recordings were not usable.

Autonomic cardiac activity during suture in pediatric emergencies

The nonparametric Mann-Whitney test showed that absolute RRI mean ($z = -3.391$; $p < 0.001$) and HF ($z = -3.06$; $p = 0.002$) were higher in the hypnosis group than in the control group. Conversely, absolute LF/HF ratio ($z = -3.338$; $p < 0.001$) was lower in the hypnosis group than in the control group without any change in absolute LF ($z = -1.2$; $p = 0.230$). Moreover, statistical analysis showed that absolute Instantaneous and Mean ANI® ($z = -3.281$; $p = 0.001$ and $z = -3.083$; $p = 0.002$, respectively) were higher in the hypnosis group than in the control group. These statistical analyses were made for all suture points, a range of 10 s before the suture and 30 s after the suture, as explained in the methods. These results are illustrated in [Figures 1 and 2](#).

The results showed that cardiac and sympathetic activity were lower, and parasympathetic activity higher under hypnosis, based on both RRI variability and ANI® analysis.

Autonomic cardiac reactivity to suture in pediatric emergencies

RM-ANOVA showed that normalized RRI was significantly different as a function of experimental conditions [$F(1,36) = 4.08$; $p = 0.051$] and as a function of time (before and after the suture) [$F(1,36) = 12.99$; $p < 0.001$], and there is an interaction between these two factors [$F(1,36) = 4.52$; $p = 0.040$]. Normalized LF was different only as a function of time [$F(1,36) = 17.65$; $p < 0.001$] but not according to experimental condition [$F(1,36) = 1.28$; $p = 0.266$] without interaction [$F(1,36) = 1.28$; $p = 0.266$].

Normalized HF was different only as a function of time [$F(1,36) = 12.55$; $p < 0.001$], but not according to experimental condition [$F(1,36) = 0.27$; $p = 0.604$] without interaction [$F(1,36) = 0.27$; $p = 0.604$]. Normalized LF/HF ratio was different as a function of time [$F(1,36) = 25.55$; $p < 0.001$] and also according to experimental condition [$F(1,36) = 7.12$; $p = 0.011$] with an interaction [$F(1,36) = 7.12$; $p = 0.012$].

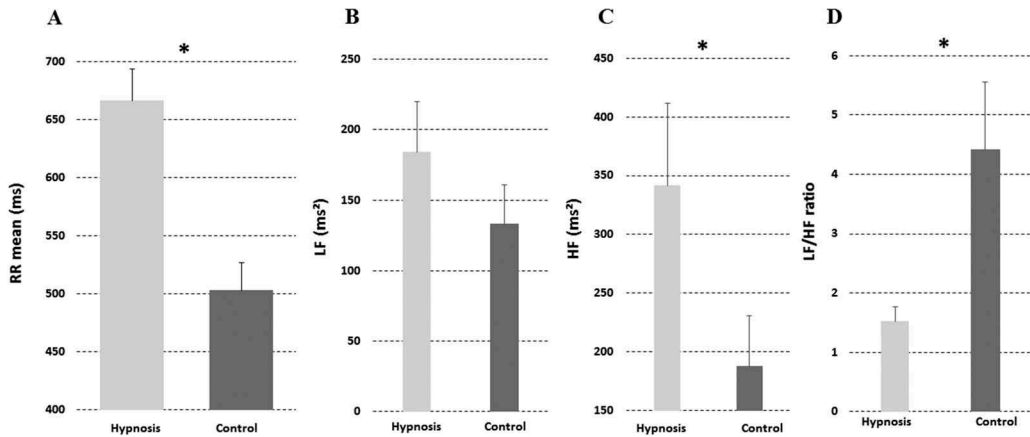


FIGURE 1. Autonomic cardiac activity during suture in children in pediatric emergencies in two experimental conditions (hypnosis group and control group), studied by absolute RR intervals and RRI variability indices. Data are presented as mean \pm SEM, $*p < 0.05$ is considered significant. A: RR intervals. B: low frequency power (LF) (ms²). C: high frequency power (HF) (ms²). D: LF/HF ratio.

RM-ANOVA showed that normalized Instantaneous and Mean ANI® were not different, neither as a function of experimental condition ($F(1,28) = 0.96$; $p = 0.337$ and $F(1,28) = 0.08$; $p = 0.779$, respectively) nor as a function of time ($F(1,28) = 0.21$; $p = 0.3649$ and $F(1,28) = 0.53$; $p = 0.473$, respectively) without interaction ($F(1,28) = 0.96$; $p = 0.337$ and $F(1,28) = 0.08$; $p = 0.779$, respectively). These results are illustrated in Figures 3 and 4.

These results showed that sutures induce cardiac and sympathetic reactivity in these children without any change in parasympathetic control, as shown by RRI variability and ANI® analysis. Moreover, this cardiac autonomic reactivity is lower under hypnosis.

Discussion

Experimental and clinical pain are well known to induce autonomic cardiac reactivity (Chouchou et al., 2011; Deschamps, Kaufman, Backman, & Plourde, 2004; Koenig, Jarczok, Ellis, Hillecke, & Thayer, 2014; Lavigne et al., 2001; Wodey et al., 2003). Moreover, experimental studies have shown that hypnosis induces parasympathetic dominance in healthy volunteers (Aubert et al., 2009; DeBenedittis et al., 1994; Diamond et al., 2008; Hippel et al., 2001). In this context, this work showed the following: (1) Hypnosis in pediatric emergencies reduces sympathetic cardiac pain reactivity; (2) parasympathetic change studied by RRI variability and ANI® analysis is rather related to hypnosis than to

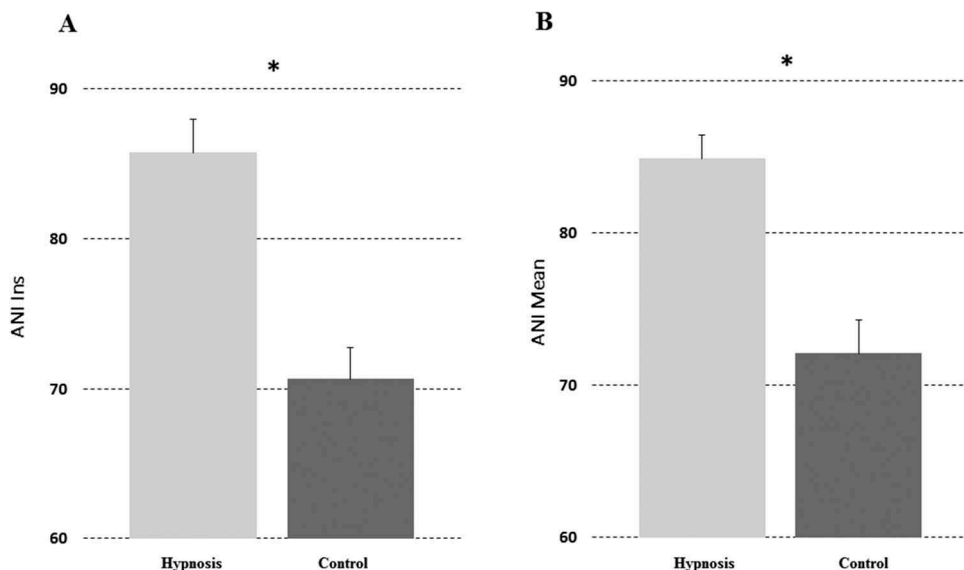


FIGURE 2. Parasympathetic cardiac activity during suture in children in pediatric emergencies in two experimental conditions (hypnosis group and control group), studied by the Analgesia and Nociception Index®. Data are presented as mean \pm SEM, $*p < 0.05$ is considered significant. A: Instantaneous Analgesia and Nociception Index. B: Mean Analgesia and Nociception Index.

the painful procedures; and (3) analysis of RR variability could provide a way to better control pain and hypnosis in pediatric emergencies.

Autonomic cardiac reactivity to painful stimulations and clinical procedures

In recent years, some experimental studies have shown that painful stimulations induced a cardiac response, underpinned by sympathetic modulation and parasympathetic withdrawal (Chouchou et al., 2011; Koenig et al., 2014; Lavigne et al., 2001). In clinical conditions, this autonomic pain reactivity was also observed, in particular, in surgical skin incisions in children (Wodey et al., 2003). In our study, using a time-frequency spectral analysis of the RRI signal, we observed an increase in cardiac sympathetic activity, without any change in parasympathetic activity in response to pain procedures in children, consistent with our previous work in experimental painful stimulations in healthy volunteers (Chouchou et al., 2011; Fauchon, Perrin, Pichot, & Peyron, 2017). While hypnosis is well known to involve dominance in parasympathetic activity in healthy controls (Aubert et al., 2009; DeBenedittis et al., 1994; Diamond et al., 2008; Hippel et al., 2001) as we reported in the present work in clinical conditions, the autonomic response to pain procedures in children is characterized by changes in sympathetic activity. In accordance with other studies (Cremillieux, Makhoulouf,

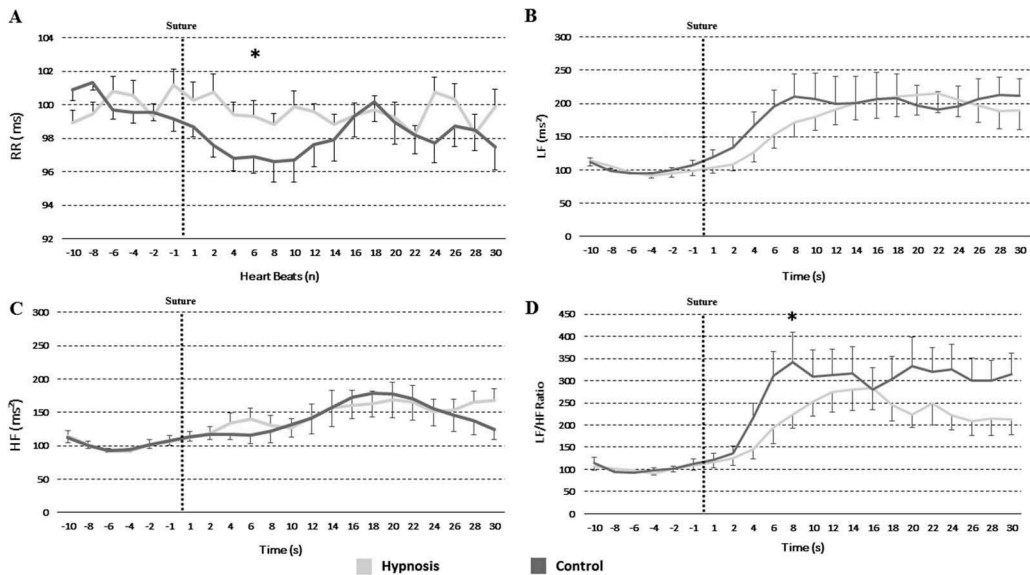


FIGURE 3. Autonomic cardiac reactivity to suture in children in pediatric emergencies in two experimental conditions (hypnosis group and control group), studied by RR intervals and the spectral power, 10 s (10 RR for RR intervals) before the suture and 30 s after the suture. Data are presented as mean \pm SEM, normalized for baseline, * $p < 0.05$ is considered significant. A: RR intervals. B: low frequency power (LF) (ms²). C: high frequency power (HF) (ms²). D: LF/HF ratio.

Pichot, Trombert, & Patural, 2018; Issa et al., 2017; Szentel et al., 2015), our study indicates that parasympathetic activity is not useful for detecting pain sensation, but can be useful as a measure of hypnotic state, as previously proposed (Diamond et al., 2008). Under hypnosis, this sympathetic pain reactivity is still present but diminished. We hypothesize that these changes in sympathetic reactivity may be related to the low pain sensation felt by patients under hypnosis (Birnie et al., 2014; Thibault-Wanquet et al., 2009; Vanhauzenhuysse et al., 2009). This is consistent with studies showing a close relationship between evoked pain and sympathetic cardiac reactivity (Treister, Klinger, Zuckerman, Goor Aryeh, & Eisenberg, 2012). These results strengthen those of previous studies (Chouchou et al., 2011; Koenig et al., 2014; Treister et al., 2012), which showed that the sympathetic reactivity to pain stimulations could be helpful for developing a marker of pain sensation. In this vein, the development of pain markers would be an important step to control pain and improve well-being of patients with the inability to communicate (e.g., Schnakers et al., 2010; Solodiuk et al., 2010). However, this sympathetic reactivity must be interpreted with caution; this reactivity can be modulated by other factors, such as stress (Widjaja, Orini, Vlemincx, & Van Huffel, 2013), placebo effect (Meissner, 2011), or emotional context (Fauchon et al., 2017, 2018). Studies are needed to expand our knowledge of sympathetic reactivity to pain, and its

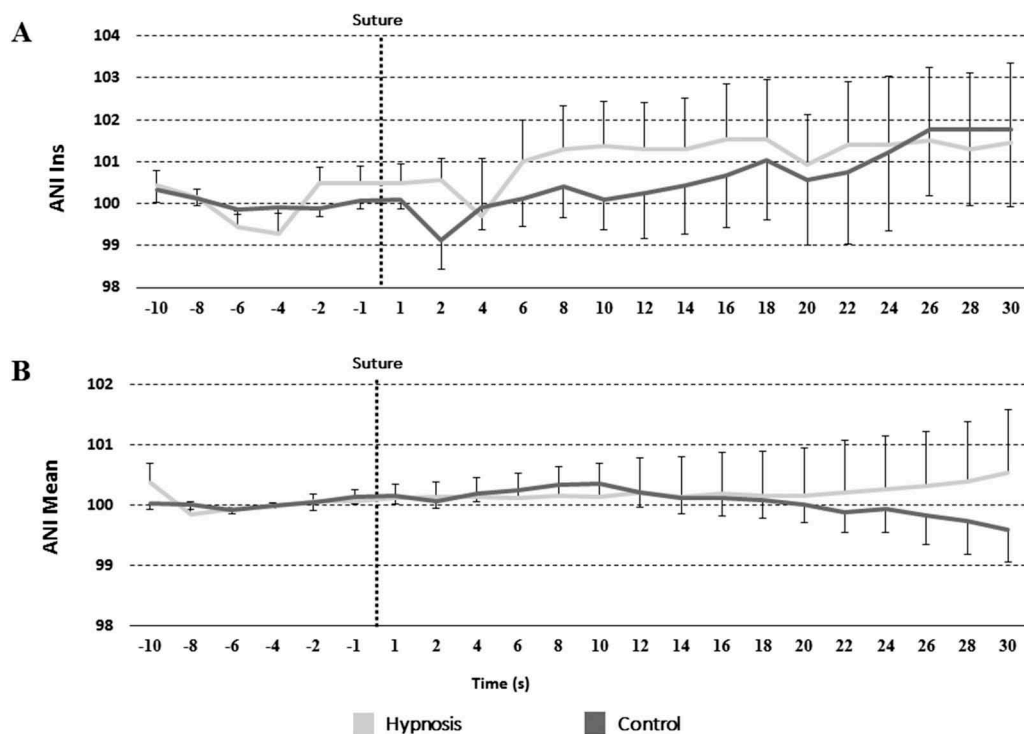


FIGURE 4 Parasympathetic cardiac reactivity to suture in children in pediatric emergencies in two experimental conditions (hypnosis group and control group), studied by the Analgesia and Nociception Index 10 s before the suture and 30 s after the suture. Data are presented as mean \pm SEM, normalized for baseline, $*p < 0.05$ is considered significant. A: Instantaneous Analgesia and Nociception Index. B: Mean Analgesia and Nociception Index in the control group. C: Mean Analgesia and Nociception Index in the hypnosis group. The parasympathetic cardiac reactivity is decreased after the suture and more in the control group.

relationship to retrospective pain and stress reports, as well as to postoperative well-being in pediatric emergencies.

Autonomic cardiac reactivity under hypnosis

We also observed that parasympathetic tone is higher in hypnosis than in the control condition. This parasympathetic dominance is consistent with previous reports in healthy volunteers (Aubert et al., 2009; DeBenedittis et al., 1994; Diamond et al., 2008; Hippel et al., 2001). This increase in parasympathetic activity under hypnosis in children in emergency situations illustrates the overall and powerful effect of hypnosis, leading to pain and anxiety relief in spite of a stressful context for these

young patients. Diamond et al. (2008) reported that self-rated hypnotic depth positively correlated with the amplitude of the HF power (parasympathetic tone) and proposed the monitoring of electrocardiography (ECG) and analysis of RR variability as a potential real-time measure of hypnotic depth. The present study expands the implications of these studies by showing that this monitoring could be feasible in pediatric emergency care.

The underlying mechanisms of these changes in autonomic activity under hypnosis remain unknown. Several mechanisms could be involved, and they might not be mutually exclusive. Hypnosis is associated with lowered arousal and altered perception in relation to top-down processes involved in the reinterpretation of the perceptual experience (Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Rainville et al., 1999). From a behavioral point of view, a subject's behavior under hypnosis is characterized by a muscular relaxation and a decrease in respiratory rate (De Pascalis & Perrone, 1996; Rainville, Feine, Bushnell, & Duncan, 1992; Ray et al., 2000). The anterior cingulate cortex seems to play a major role in these physiological and behavioral hypnotic responses (Jensen et al., 2017) and pain perception under hypnosis (Faymonville et al., 2000b). The cingulate cortex is also considered to be one of the key cortical structures of the autonomic central network (Critchley & Harrison, 2013; Ruiz Vargas, Sörös, Shoemaker, & Hachinski, 2016), which controls autonomic activity. Thus, changes in activity of the cingulate cortex could be the cause of changes in autonomic activity under hypnosis but also somatic and behavioral changes such as respiratory deceleration and muscle relaxation (Machado, 2013). Further studies are needed to confirm these hypotheses.

Limitations

The main limitation of this study is the lack of random assignment. However, in clinical emergency conditions, the choice of the child is necessary. A future randomized study is needed to overcome this limitation of this first study. Furthermore, pain sensation was not assessed by the children during their medical care with self-rating scales such as VAS (Bailey et al., 2012). Thus, no comparisons between these assessments and the results at each suture point were performed. However, the decrease in pain perception is well documented (Faymonville et al., 2000a; Rainville et al., 1999, 1999; Vanhaudenhuyse et al., 2009) and frequently used in pain management in children (Thibault-Wanquet et al., 2009).

Conclusions

The present study showed that it is possible to assess sympathetic reactivity to pain and parasympathetic changes due to hypnosis using RR variability in pediatric emergencies. The study is also consistent with previous works, showing that hypnosis during painful procedures in pediatric emergencies decreases sympathetic cardiac pain reactivity. Conversely, parasympathetic changes studied by RRI variability and ANI®

analysis seem to rather be related to states of consciousness such as hypnosis. Sympathetic cardiac reactivity could be helpful for developing a marker of pain sensation in pediatric emergencies, while parasympathetic activity seems to be a better marker of hypnosis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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