



HAL
open science

Autonomic response to fetal acidosis using an experimental sheep model

Roxane Vanspranghels, Julien de Jonckheere, Elodie Drumez, Arthur Lauriot Dit Prevost, Dyuti Sharma, Louise Ghesquiere, Laurent Storme, Véronique Houfflin-Debarge, Charles Garabedian

► **To cite this version:**

Roxane Vanspranghels, Julien de Jonckheere, Elodie Drumez, Arthur Lauriot Dit Prevost, Dyuti Sharma, et al.. Autonomic response to fetal acidosis using an experimental sheep model. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2020, 246, pp.151 - 155. 10.1016/j.ejogrb.2020.01.018 . hal-03489769

HAL Id: hal-03489769

<https://hal.science/hal-03489769>

Submitted on 21 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Autonomic response to fetal acidosis using an experimental sheep model

1 **Roxane Vanspranghels**^{1,2}, **Julien De Jonckheere**^{1,3}, **Elodie Drumez**⁴, **Arthur Lauriot dit**
2 **Prevost**^{1,5}, **Dyuti Sharma**^{1,5}, **Louise Ghesquiere**^{1,2}, **Laurent Storme**^{1,6}, **Véronique**
3 **Houfflin-Debarge**^{1,2}, **Charles Garabedian**^{1,2}

4 ¹ University of Lille, EA 4489 – Perinatal Environment and Health, F-59000 Lille, France

5 ² CHU Lille, Department of Obstetrics, F-59000 Lille, France

6 ³ CHU Lille, CIC-IT 1403, F-59000 Lille, France

7 ⁴ University of Lille, CHU Lille, EA 2694 – Public health: epidemiology and quality of care,
8 Department of Biostatistics, F-59000 Lille, France

9 ⁵ CHU Lille, Department of Pediatric Surgery, F-59000 Lille, France

10 ⁶ CHU Lille, Department of Neonatology, F-59000 Lille, France

11 *** Correspondence:**

12 Dr Charles Garabedian

13 charles.garabedian@chru-lille.fr

14 **Keywords: fetal sheep, acidosis, heart rate variability, autonomic nervous system, labor**
15 **monitoring.**

16

17 **Short title:** Sheep fetal autonomic nervous system response to acidosis

18

19 **ABSTRACT**

20 **Background:** The autonomic nervous system has a major role in fetal adaptation to hypoxia.
21 Its activity might be assessed using heart rate variability and heart rate deceleration analyses.

22 **Objective:** To evaluate the ability of different heart rate variability and morphological
23 deceleration analyses to predict fetal acidosis during labor in an experimental fetal sheep
24 model.

25 **Study Design:** Repeated 1-minute total umbilical cord occlusions were performed at mild (1
26 minute every 5 minutes), moderate (1 minute every 3 minutes), and severe (1 minute every 2
27 minutes) umbilical cord occlusion periodicities until arterial pH reached 7.10. Hemodynamic,
28 blood gas analysis, morphological analysis of decelerations (magnitude, slope, and area of
29 decelerations), and heart rate variability parameters were recorded throughout the experiment.
30 Heart rate variability analysis included temporal analysis (root mean square of successive
31 differences between adjacent R-R intervals, standard deviation of normal to normal R-R
32 intervals, short term variability), spectral analysis (low frequencies, high frequencies,
33 normalized high frequencies), and a new index developed by our team, the Fetal Stress Index.
34 We defined and compared three pH groups: >7.20, 7.10–7.20, and <7.10.

35 **Results:** Eleven experiments were performed. Repetitive umbilical cord occlusions resulted
36 in progressive fetal acidosis. Fetal Stress Index was correlated with pH and lactate ($p < 0.05$)
37 and increased with acidosis. There were no significant correlations between pH, lactate, and
38 other indices (spectral analysis, temporal analysis, or morphological analysis of
39 decelerations).

40 **Conclusion:** This protocol allowed us to identify the progressive onset of fetal acidosis in an
41 experimental model close to labor. Fetal Stress Index is a heart rate variability method that
42 varies with acidosis and indicates an increase in parasympathetic nervous system activity in
43 response to fetal acidosis.

44

45 INTRODUCTION

46 During labor, a decrease in maternofetal gas exchange can lead to fetal acidosis, which
47 can cause severe neonatal complications, including a risk of cerebral palsy. Almost 10% of
48 cerebral palsy is induced by peripartum asphyxia (1). Currently, fetal wellbeing is assessed
49 using fetal heart rate (FHR) analysis, subject to high intra- and inter-observer variability, and
50 imperfectly reflecting fetal oxygenation (2,3). There is a need for development of new tools for
51 evaluation of fetal wellbeing and analysis of autonomic nervous system (ANS) activity may
52 help optimize diagnosis.

53 Indeed, the ANS plays a major role in fetal homeostasis (4,5). Heart rate is under ANS
54 influence (6) through chemoreceptors and baroreceptors, and vary constantly according to
55 fetal homeostasis (7). Heart rate variability (HRV) is therefore an efficient way to study ANS
56 activity. Many HRV analysis techniques have been described. Time domain analysis includes
57 indices such as standard deviation of normal to normal R-R intervals (SDNN), root mean
58 square of successive differences between adjacent R-R intervals (RMSSD), or short-term
59 variability (STV), the latter being specially developed for fetal HRV analysis (8). Frequency
60 (or spectral) analysis consists of a time frequency transformation, which distinguishes: very
61 low frequencies reflecting thermoregulation and endocrine activity, low frequencies (LF)
62 reflecting sympathetic and parasympathetic activities associated with the baroreflex, and high
63 frequencies (HF) specifically linked to parasympathetic activity (9). Variations in these HRV
64 indices have been studied in acidosis situations with inconsistent results (4,10).

65 Traditional FHR analysis relies on deceleration classification, associated with
66 variability and baseline rate (11). Cahill et al. even focused on deceleration cumulative effects
67 on acidosis occurrence (12). HRV analysis combined with deceleration analysis may provide
68 a complementary method toward quantifying fetal status.

69 Our team has developed a new index, the Fetal Stress Index (FSI), based on an
70 original HRV analysis method (13). In previous experimental studies, we demonstrated that
71 the FSI reflects parasympathetic fluctuation (14,15) and that the FSI is correlated with
72 acidosis in a fetal sheep model of continuous umbilical cord occlusion (UCO), and in a
73 repeated 1 minute total UCO every 2.5 minutes model (11,16). Nonetheless, that protocol was
74 distinct from the labor physiology and was focused on only our marker. Other HRV markers
75 and aspect of deceleration were not simultaneously evaluated.

76 Therefore, our objective was to evaluate different HRV analysis methods and
77 morphology of decelerations' ability to reflect fetal acid-basis status in an experimental model
78 of cord occlusions reproducing the different stages of labor.

79

80 **METHODS**

81 **Ethics**

82 The anesthesia, surgery, and experimentation protocols were consistent with the
83 recommendations of the Ministry of Higher Education and Research, and the study was
84 approved by the Animal Experimentation Ethics Committee (CEEA #2016121312148878).

85 **Surgical preparation**

86 Near-term pregnant sheep (race 'Ile de France', Tours'INRA, Orfrasière animal
87 physiology experimental Unit, Val de Loire Center) with a gestational age of 124 ± 1 days
88 (term = 145 days) underwent our previously described surgical procedure (11,12,16).

89 Briefly, under general anesthesia, after maternal laparotomy and hysterotomy,
90 catheters (4Fr diameter, Arrow©, USA) were placed in the fetal right axillary artery and vein
91 and in the left axillary artery. Four electrocardiogram (ECG) electrodes (Mywire 10©,
92 Maquet, Rastatt, Germany) were placed on the fetal intercostal muscles near the heart to
93 record fetal ECG. An inflatable silicone occluder (OC16; In Vivo Metric, Healdsburg, CA)
94 was placed around the umbilical cord.

95 **HRV analysis**

96 ECG analysis for fetal RR series computation was conducted offline using an
97 automatic R-wave detection algorithm. HRV time domain analyses included RMSSD, SDNN,
98 and STV, defined as the mean difference between successive 3.75 seconds R-R interval
99 epochs. RMSSD and STV are related to parasympathetic nervous system activity whereas
100 SDNN evaluates ANS global activity (8).

101 Spectral HRV analysis included the LF component, from 0.04 to 0.15 Hz, related to
102 both sympathetic and parasympathetic activity, and also associated with baroreflex activity.
103 We also studied the HF component, superior to 0.15 Hz, related only to the parasympathetic
104 nervous system. The HF normalized value traduced the imbalance between parasympathetic

105 and sympathetic, and was also computed as $HF_{nu} = HF/(HF+LF)$. We have previously
106 described the algorithm used to compute the FSI (15,17–19). Continuous computation of the
107 HRV indexes is assumed by sliding the moving window with a 1-second moving period.
108 Indices are then at an average over 3 minutes.

109 **Morphologic analysis of FHR deceleration**

110 Morphologic deceleration analysis included duration (defined by the time needed to
111 recover FHR measured before the deceleration, or, if not reached, the time to recover a stable
112 FHR baseline), magnitude (from beginning to nadir), and slope (amplitude/duration). As
113 described by Cahill et al., the deceleration's total area was also evaluated as ($\frac{1}{2} \times$ duration \times
114 magnitude) (12).

115 **Experimental procedure**

116 Experiments began four days post-surgery. A 60-minute period without any stimulus
117 was recorded to ensure fetal stability (normal gas blood and hemodynamic parameters).
118 Injection of saline solution inside the occluder allowed complete cord occlusion. The protocol
119 was divided into three phases, each lasting one hour, as described by Prout et al. (20). During
120 the first hour, a mild UCO series was performed consisting of 1-minute cord occlusions
121 repeated every 5 minutes. During the second hour, a moderate UCO series was performed
122 consisting of 1-minute cord occlusions repeated every 3 minutes. During the third hour, a
123 severe UCO series was performed consisting of 1-minute cord occlusions repeated every 2
124 minutes. For each stage, 5-minute periods with no UCO were observed at 20, 40, and 60
125 minutes for blood samples and hemodynamic and HRV indexes analyses. Morphologic
126 deceleration analysis was performed on the last deceleration before the 5-minute period.

127 **Statistical analysis**

128 Qualitative values were described in term of frequency and percentage. Gaussian
129 numerical values were described in term of mean and standard error. Normality of numerical

130 values were checked graphically and tested using the Shapiro–Wilk test. Three pH groups
131 were defined: >7.20 (group A), 7.10–7.20 (group B), and <7.10 (group C). Associations
132 between indices and pH groups were studied using a mixed linear model, including pH group
133 and time as fixed effects, and fetal sheep as a random effect. Linear contrasts were identified
134 based on post-hoc trends to determine whether the relations between markers and pH groups
135 were linear. Correlations between different markers and pH, and lactate and base excess were
136 evaluated at each time point using a mixed linear model with marker and time as fixed effects,
137 and fetal sheep and number of manipulations for each lamb as random effects. The normality
138 of residuals for each model was checked graphically. Bivariate tests required an alpha level of
139 5% to be considered statistically significant. When a correlation was significant, a ROC
140 analysis was performed to study the ability of the FSI to detect $\text{pH} \leq 7.20$ and $\text{pH} \leq 7.10$.
141 Statistical analyses were conducted using SAS software (SAS Institute 9.4, Cary, USA).

142

143 **RESULTS**

144 Eleven healthy fetal sheep underwent surgery. The protocol was interrupted due to pH
145 <7.10 after one hour of the mild stage occlusion for three fetal sheep, during the moderate
146 stage for another three, and during the intensive stage for another three sheep. Only two fetal
147 sheep underwent the complete three-period UCO protocol.

148 Table 1 shows variation in recorded parameters according to pH. Mean heart rate was
149 174.4 bpm (\pm 8.9) in group A vs 193 bpm (\pm 3.4) in group C ($p=0.06$). No significant
150 correlation between heart rate and blood gas status was observed (pH, lactate or base excess)
151 (Table 2). MAP (mean arterial pressure) was significantly increased in group C (62.3 ± 3.4
152 mmHg) compared with group B (57.5 ± 3.2 mmHg), which was also higher compared with
153 group A (53.2 ± 3.2 mmHg) ($p=0.048$) (Table 1). MAP was also correlated with pH ($\beta \pm$
154 SEM -0.003 ± 0.001 , $p=0.006$), lactate ($\beta \pm$ SEM = 0.079 ± 0.026 , $p=0.004$), and base excess
155 ($\beta \pm$ SEM = -0.110 ± 0.051 , $p=0.036$).

156 The FSI increased progressively from $61.4 (\pm 3.8)$ to $65.3 (\pm 3.7)$ until reaching 77.1
157 (± 3.9) in the group C ($p<0.001$) (Table 1). The FSI was correlated with pH and lactate
158 ($p<0.001$ and 0.015) (Table 2). The AUC (area under curve) for FSI to distinguish $pH \geq 7.20$
159 vs $pH <7.20$ was at 0.711 , whereas AUC was 0.903 when separating $pH > 7.10$ vs $pH \leq 7.10$
160 (Fig. 1). RMSSD, SDNN, STV, LF, HF, and HFnu did not differ significantly between pH
161 groups (Table 1) and were not significantly correlated with blood gas variations (Table 2).
162 SDNN increased progressively from $14.7 (\pm 3)$ in the group A, to $15.3 (\pm 2.9)$ in group B until
163 $20.7 (\pm 3.1)$, and in the group with group C; however, this increase was not significant
164 ($p=0.083$) (Table 1). SDNN was not significantly correlated with lactate or base excess (Table
165 2).

166 Concerning morphological deceleration analysis, a moderate increase in FHR
167 magnitude of decelerations was observed between group A ($2.88 \text{ bpm/s} \pm 0.54$) and group B

168 (4.12 bpm/s \pm 0.52) but this difference was not statistically significant (p=0.068) (Table 1).

169 No significant correlation between deceleration slopes or total area deceleration with gas

170 blood parameters was observed (Table 2).

171

172 **DISCUSSION**

173 The aim of fetal monitoring during labor is to detect the fetus at risk of acidosis. ANS
174 analysis may be a promising area of research due to its major role in maintaining fetal
175 homeostasis. Different indices for evaluating ANS activity exist, though their correlations
176 with fetal acidosis are still being evaluated. In the current study, we have demonstrated that
177 the FSI, which reflects parasympathetic fluctuations, increased with the onset of acidosis,
178 whereas heart rate, SDNN, and deceleration slopes tended to increase when acidosis
179 appeared. RMSSD, STV, LF, HF, and HFnu, and total area of decelerations were not
180 significantly correlated with acidosis in our experimental model.

181 Different ANS analysis methods have been proposed. HRV time domain analysis
182 relies on indices such as RMSSD, SDNN, or STV, which are well known by obstetricians
183 (21–24). RMSSD reflects short-term HRV variations and vagal responses to stimulus (25).
184 Frasch et al. described RMSSD increases during cord occlusion, each lasting 4 minutes and
185 repeated every 30 minutes (9). Frasch et al. also emphasized that RMSSD increase was
186 associated with cerebral adaptive mechanisms seen in cord occlusions (26). The idea that
187 RMSSD may reflect cerebral inflammation was strengthened by Yamaguchi et al. In Humans,
188 data are only available postnatally, after the anoxic event, with a relationship shown between
189 RMSSD decrease and severe brain lesions or EEG grades (28,29). In our study, acidosis level
190 remained moderate, only occurring at the end of the protocol. Cerebral consequences may,
191 thus, just begin, without neuronal death. SDNN reflects global ANS tonus (25); in our study,
192 we noticed a trend toward progressive increase in SDNN while pH decreased, showing a
193 global ANS activation between each deceleration. As for RMSSD, in severe, long occlusions
194 associated with ischemia and cerebral lesions, SDNN is first abolished, then highly increased
195 compared with controls, before decreasing at six hours (27). In Humans, data only exist for
196 the postnatal period, with a decrease in SDNN linked to EEG severity (28).

197 STV is used in growth restricted fetuses and interest in it during labor has been
198 discussed (30). A meta-analysis has shown a moderate capacity for STV to predict acidosis
199 with a sensitivity of 0.57 (95% CI: 0.45–0.68) and a specificity of 0.81 (95% CI: 0.69–0.89)
200 (21). Our model showed a progressive increase in STV when pH decreased, though this was
201 not statistically significant. This is consistent with others' findings on STV during labor (19).
202 Lu et al. noticed an STV elevation when lactate increased during labor (24); in acidosis cases
203 (lactate >4.8 mmol/L), median STV 30 minutes prior to fetal blood sample was 7.10
204 milliseconds compared with 6.09 milliseconds in the pre-acidosis (4.2–4.8 mmol/L) and 5.23
205 milliseconds in the normal (<4.2 mmol/L) groups ($p<.05$).

206 Spectral analysis is another way to evaluate HRV. Chung et al. performed spectral
207 analysis during the last two hours before birth and observed a diminution of every index in
208 fetuses with acidosis. Siira et al. noticed that in the last hour of labor, LF and HF increased in
209 every fetus ($N=334$) and decreased near birth in fetuses with pH under 7.05 (31). Van Laar et
210 al. found an increase in LFnu and a decrease in HFnu during the last 30 minutes of labor
211 when pH <7.05 at birth (32). Such studies are of interest as they show different modification
212 of the HRV index in cases with acidosis, though with inconsistent results. This may be due to
213 different timings of analysis. Indeed, Warmerdam et al. (33) focused on analyses based on
214 externally recorded contractions in order to gain better ECG signals and avoid mathematical
215 artefacts linked to decelerations. In our study, we did not find any statistically significant
216 associations between LF, HF, or HFnu, although these indices varied between pH groups.

217 Morphologic deceleration analysis might be another valuable tool to evaluate fetal
218 physiologic response to acidosis, as proposed in the FIGO guidelines (34). Cahill et al. also
219 evaluated the total area of deceleration during the last two hours of labor in 8580 term fetuses
220 (12) to show this as a discriminative indicator for suspecting fetal acidosis with a pH <7.10
221 (AUC 0.76, IC95% [0.72–0.80]). In our experimental study, we did not find a significant

222 correlation between morphologic deceleration analysis and acidosis. This could be explained
223 by the fact that our protocol stopped after reaching pH <7.10.

224 Our HRV method, already used in adult and newborn monitoring (35,36), has been
225 adapted to propose a physiological tool reflecting the fetal parasympathetic activity. In
226 previous experimental studies, we have demonstrated that the FSI is associated with lower
227 inter-individual variability and a higher effect size than commonly used HRV analysis
228 methods, suggesting that it may be better to detect parasympathetic variations (13). In the
229 present study, the FSI was the only index of HRV significantly associated with variations in
230 pH and lactate. These results confirm the important implications of the parasympathetic
231 nervous system for fetal adaptation to hypoxia (37), as previously described by Lear et al.
232 (38). Using such an index may allow a more physiologic approach to fetal monitoring.

233 This experimental study had some limits. Although we used an animal model
234 resembling human gestation, reproducibility of our physiologic findings and their applications
235 to human fetuses must be carefully established. It is still premature to develop in current
236 clinical practice at this time. However, with the improvement of fetal ECG recording systems
237 and thus of R-R signal quality, we can imagine a clinical application in the automated analysis
238 of the fetal heart rate (baseline, characteristics of decelerations) and the heart rate variability,
239 reflecting fluctuations of the autonomous nervous system. Therefore, it is important to
240 continue this experimental project to better understand physiological mechanisms, while
241 starting preliminary studies in humans. Fetal hypoxia was obtained through umbilical cord
242 compression as described in previous studies from others teams. It reflects a part of the
243 mechanism of hypoxia during contraction also caused by compression of uteroplacental
244 vessels. Finally, others indices approached statistical significance and it will be interesting to
245 evaluate in a larger study.

246

247

248 **CONCLUSIONS**

249 HRV is an interesting tool to detect fetal acidosis during labor, as it reflects ANS
250 modulations and, thus, allows a more physiologic approach to fetal monitoring. The new
251 index developed by our team, the FSI, is the only discriminative HRV index to detect
252 acidosis. These findings strongly suggest that changes in the parasympathetic nervous system
253 may reflect progressive fetal asphyxia. It will be of interest to replicate these findings using an
254 animal model to assess the risk of anoxic cerebral lesions.

255

256 **ACKNOWLEDGEMENTS**

257 We thank Capucine Besengez and all the staff of the Research Experimental Department of University
258 Lille North of France for their veterinary care and their expert assistance with sheep surgery.

259

260

261 **REFERENCES**

- 262 1. Low JA, Galbraith RS, Muir DW, Killen HL, Pater EA, Karchmar EJ. Factors associated with
263 motor and cognitive deficits in children after intrapartum fetal hypoxia. *Am J Obstet Gynecol.*
264 1984 Mar 1;148(5):533–9.
- 265 2. Everett TR, Peebles DM. Antenatal tests of fetal wellbeing. *Semin Fetal Neonatal Med.* 2015
266 Jun;20(3):138–43.
- 267 3. Rei M, Tavares S, Pinto P, Machado AP, Monteiro S, Costa A, et al. Interobserver agreement in
268 CTG interpretation using the 2015 FIGO guidelines for intrapartum fetal monitoring. *Eur J*
269 *Obstet Gynecol Reprod Biol.* 2016 Oct;205:27–31.
- 270 4. Siira SM, Ojala TH, Vahlberg TJ, Rosén KG, Ekholm EM. Do spectral bands of fetal heart rate
271 variability associate with concomitant fetal scalp pH? *Early Hum Dev.* 2013 Sep;89(9):739–42.
- 272 5. Van Laar JOEH, Porath MM, Peters CHL, Oei SG. Spectral analysis of fetal heart rate
273 variability for fetal surveillance: review of the literature. *Acta Obstet Gynecol Scand.*
274 2008;87(3):300–6.
- 275 6. Garabedian C, De Jonckheere J, Butruille L, Deruelle P, Storme L, Houfflin-Debarge V.
276 Understanding fetal physiology and second line monitoring during labor. *J Gynecol Obstet Hum*
277 *Reprod.* 2017 Feb 1;46(2):113–7.
- 278 7. Rosén KG, Kjellmer I. Changes in the fetal heart rate and ECG during hypoxia. *Acta Physiol*
279 *Scand.* 1975 Jan;93(1):59–66.
- 280 8. Canm, John ; Bigger, Thomas ; Heart rate variability. Standards of measurement, physiological
281 interpretation, and clinical use. Task Force of the European Society of Cardiology and the North
282 American Society of Pacing and Electrophysiology. *Eur Heart J.* 1996 Mar;17(3):354–81.
- 283 9. Frasch MG, Müller T, Weiss C, Schwab K, Schubert H, Schwab M. Heart rate variability
284 analysis allows early asphyxia detection in ovine fetus. *Reprod Sci Thousand Oaks Calif.* 2009
285 May;16(5):509–17.
- 286 10. van Laar JOEH, Peters CHL, Vullings R, Houterman S, Bergmans JWM, Oei SG. Fetal
287 autonomic response to severe acidemia during labour. *BJOG Int J Obstet Gynaecol.* 2010
288 Mar;117(4):429–37.
- 289 11. Ayres-de-Campos D, Arulkumaran S, FIGO Intrapartum Fetal Monitoring Expert Consensus
290 Panel. FIGO consensus guidelines on intrapartum fetal monitoring: Physiology of fetal
291 oxygenation and the main goals of intrapartum fetal monitoring. *Int J Gynaecol Obstet Off*
292 *Organ Int Fed Gynaecol Obstet.* 2015 Oct;131(1):5–8.
- 293 12. Cahill AG, Tuuli MG, Stout MJ, López JD, Macones GA. A prospective cohort study of fetal
294 heart rate monitoring: deceleration area is predictive of fetal acidemia. *Am J Obstet Gynecol.*
295 2018 May 1;218(5):523.e1-523.e12.
- 296 13. Garabedian C, Champion C, Servan-Schreiber E, Butruille L, Aubry E, Sharma D, et al. A new
297 analysis of heart rate variability in the assessment of fetal parasympathetic activity: An
298 experimental study in a fetal sheep model. *PloS One.* 2017;12(7):e0180653.
- 299 14. Garabedian C, Aubry E, Sharma D, Bleu G, Clermont-Hama Y, Ghesquière L, et al. Exploring
300 fetal response to acidosis in ewes: Choosing an adequate experimental model. *J Gynecol Obstet*
301 *Hum Reprod.* 2018 Apr 11

- 302 15. Garabedian C, Clermont-Hama Y, Sharma D, Aubry E, Butruille L, Deruelle P, et al. Correlation
303 of a new index reflecting the fluctuation of parasympathetic tone and fetal acidosis in an
304 experimental study in a sheep model. PLoS ONE [Internet]. 2018 Jan 10 [cited 2018 Feb
305 28];13(1).
- 306 16. Ghesquière L, De Jonckheere J, Drumez E, Sharma D, Aubry E, Deruelle P, et al.
307 Parasympathetic nervous system response to acidosis: Evaluation in an experimental fetal sheep
308 model. *Acta Obstet Gynecol Scand*. 2019 Apr;98(4):433–9.
- 309 17. Garabedian C, Clermont-Hama Y, Sharma D, Aubry E, Butruille L, Deruelle P, et al. Correlation
310 of a new index reflecting the fluctuation of parasympathetic tone and fetal acidosis in an
311 experimental study in a sheep model. *PloS One*. 2018;13(1):e0190463.
- 312 18. Butruille L, Jonckheere JD, Flocteil M, Garabedian C, Houfflin-Debargé V, Storme L, et al.
313 Parasympathetic tone variations according to umbilical cord pH at birth: a computerized fetal
314 heart rate variability analysis. *J Clin Monit Comput*. 2017 Dec 1;31(6):1197–202.
- 315 19. Garabedian C, Butruille L, Servan-Schreiber E, Ficheur G, Storme L, Deruelle P, et al. Fetal
316 Heart-Rate Variability: Validation of a New Continuous, Noninvasive Computerized Analysis.
317 *Gynecol Obstet Invest*. 2017;82(5):500–7.
- 318 20. Prout AP, Frasch MG, Veldhuizen RAW, Hammond R, Ross MG, Richardson BS. Systemic and
319 cerebral inflammatory response to umbilical cord occlusions with worsening acidosis in the
320 ovine fetus. *Am J Obstet Gynecol*. 2010 Jan;202(1):82.e1-9.
- 321 21. Kapaya H, Jacques R, Rahaim N, Anumba D. “Does short-term variation in fetal heart rate
322 predict fetal acidemia?” A systematic review and meta-analysis. *J Matern Fetal Neonatal Med*.
323 2016 Dec 16;29(24):4070–7.
- 324 22. Frusca T, Todros T, Lees C, Bilardo CM, TRUFFLE Investigators. Outcome in early-onset fetal
325 growth restriction is best combining computerized fetal heart rate analysis with ductus venosus
326 Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. *Am J Obstet Gynecol*.
327 2018 Feb;218(2S):S783–9.
- 328 23. Aernout EM, Devos P, Deruelle P, Houfflin-Debargé V, Subtil D. Short-Term Variation of the
329 Fetal Heart Rate for Predicting Neonatal Acidosis in Preeclampsia. *Fetal Diagn Ther*.
330 2015;38(3):179–85.
- 331 24. Lu K, Holzmann M, Abtahi F, Lindecrantz K, Lindqvist PG, Nordstrom L. Fetal heart rate short
332 term variation during labor in relation to scalp blood lactate concentration. *Acta Obstet Gynecol*
333 *Scand*. 2018 May 25;
- 334 25. Ernst G. Hidden Signals—The History and Methods of Heart Rate Variability. *Front Public*
335 *Health* [Internet]. 2017 [cited 2018 May 25];5.
- 336 26. Frasch MG, Szykaruk M, Prout AP, Nygard K, Cao M, Veldhuizen R, et al. Decreased
337 neuroinflammation correlates to higher vagus nerve activity fluctuations in near-term ovine
338 fetuses: a case for the afferent cholinergic anti-inflammatory pathway? *J Neuroinflammation*.
339 2016 May 10
- 340 27. Yamaguchi K, Lear CA, Beacom MJ, Ikeda T, Gunn AJ, Bennet L. Evolving changes in fetal
341 heart rate variability and brain injury after hypoxia-ischaemia in preterm fetal sheep. *J Physiol*.
342 2018 Jan 8;

- 343 28. Goulding RM, Stevenson NJ, Murray DM, Livingstone V, Filan PM, Boylan GB. Heart rate
344 variability in hypoxic ischemic encephalopathy during therapeutic hypothermia. *Pediatr Res.*
345 2017 Apr;81(4):609–15.
- 346 29. Metzler M, Govindan R, Al-Shargabi T, Vezina G, Andescavage N, Wang Y, et al. Pattern of
347 brain injury and depressed heart rate variability in newborns with hypoxic ischemic
348 encephalopathy. *Pediatr Res.* 2017 Sep;82(3):438–43.
- 349 30. Serra V, Moulden M, Bellver J, Redman CWG. The value of the short-term fetal heart rate
350 variation for timing the delivery of growth-retarded fetuses. *BJOG Int J Obstet Gynaecol.* 2008
351 Aug;115(9):1101–7.
- 352 31. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Välimäki IA, Rosén KG, et al. Marked fetal
353 acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded
354 during the last hour of labour. *BJOG Int J Obstet Gynaecol.* 2005 Apr;112(4):418–23.
- 355 32. van Laar JOEH, Peters CHL, Vullings R, Houterman S, Oei SG. Power spectrum analysis of
356 fetal heart rate variability at near term and post term gestation during active sleep and quiet
357 sleep. *Early Hum Dev.* 2009 Dec;85(12):795–8.
- 358 33. Warmerdam GJJ, Vullings R, Laar JOEHV, Jagt MBV der H-V der, Bergmans JWM, Schmitt L,
359 et al. Using uterine activity to improve fetal heart rate variability analysis for detection of
360 asphyxia during labor. *Physiol Meas.* 2016;37(3):387.
- 361 34. Ayres-de-Campos D, Spong CY, Chandraran E, FIGO Intrapartum Fetal Monitoring Expert
362 Consensus Panel. FIGO consensus guidelines on intrapartum fetal monitoring:
363 Cardiotocography. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet.* 2015
364 Oct;131(1):13–24.
- 365 35. Rakza T, Butruille L, Thirel L, Houfflin-Debargé V, Logier R, Storme L, et al. Short-term
366 Impact of Assisted Deliveries: Evaluation Based on Behavioral Pain Scoring and Heart Rate
367 Variability. *Clin J Pain.* 2018 May;34(5):445–9.
- 368 36. Jeanne M, Delecroix M, De Jonckheere J, Keribedj A, Logier R, Tavernier B. Variations of the
369 analgesia nociception index during propofol anesthesia for total knee replacement. *Clin J Pain.*
370 2014 Dec;30(12):1084–8.
- 371 37. Lear CA, Galinsky R, Wassink G, Mitchell CJ, Davidson JO, Westgate JA, et al. Sympathetic
372 neural activation does not mediate heart rate variability during repeated brief umbilical cord
373 occlusions in near-term fetal sheep. *J Physiol.* 2016 Mar 1;594(5):1265–77.
- 374 38. Lear CA, Galinsky R, Wassink G, Yamaguchi K, Davidson JO, Westgate JA, et al. The myths
375 and physiology surrounding intrapartum decelerations: the critical role of the peripheral
376 chemoreflex. *J Physiol.* 2016 01;594(17):4711–25.
- 377

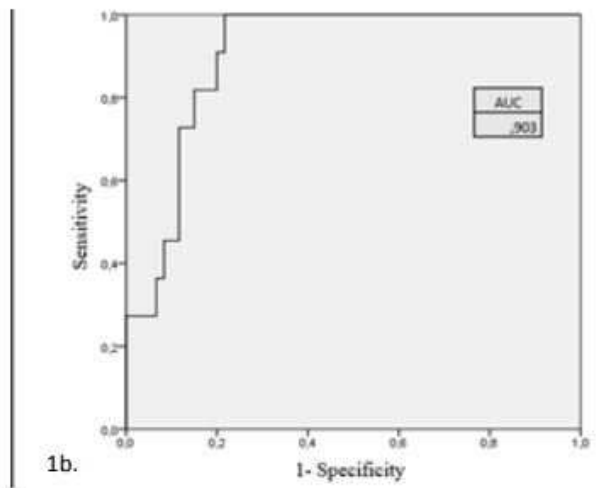
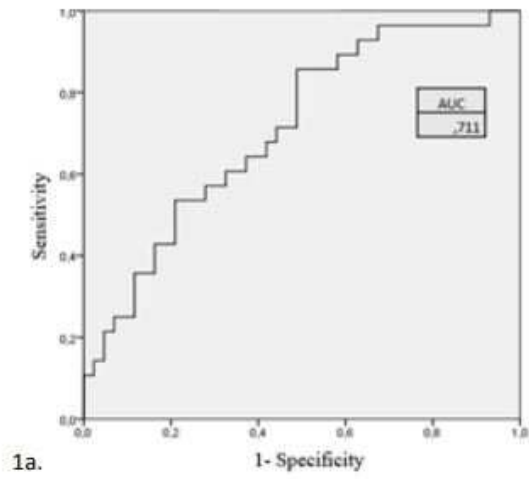
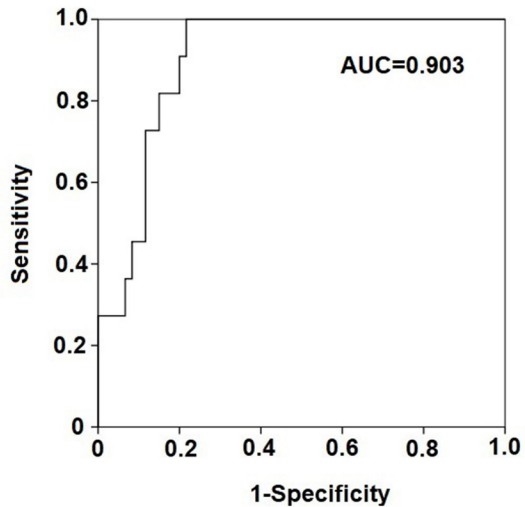
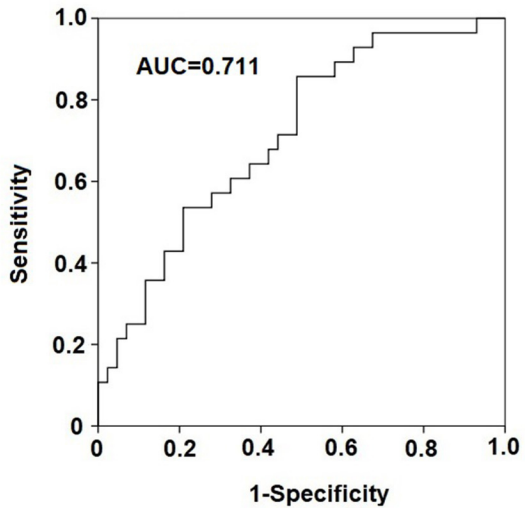


Fig. 1: ROC curves for FSI accuracy to predict acidosis.

1a: pH < 7.20 vs pH ≥ 7.20

1b: pH < 7.10 vs pH ≥ 7.10



	pH group			<i>P</i>
	<7.10	7.10–7.20	>7.20	
n	11	17	44	
FHR (bpm)	193.1 ± 9.2	173.5 ± 8.5	174.4 ± 8.9	0.066
MAP (mmHg)	62.3 ± 3.4	57.5 ± 3.2	53.2 ± 3.2	0.016
RMSSD	21.1 ± 4.2	13.1 ± 4.1	14.8 ± 1.1	0.13
SDNN	20.7 ± 3.1	15.3 ± 2.9	14.7 ± 3.0	0.083
STV	5.03 ± 0.83	4.49 ± 0.77	3.80 ± 0.78	0.21
LF	0.37 ± 0.10	0.09 ± 0.10	0.18 ± 0.10	0.13
HF	0.23 ± 0.08	0.05 ± 0.07	0.12 ± 0.01	0.25
HFnu	0.31 ± 0.04	0.31 ± 0.03	0.33 ± 0.03	0.76
FSI	77.1 ± 3.9	65.3 ± 3.7	61.4 ± 3.8	<0.001
Amplitude (bpm)	92.4 ± 10.6	108.1 ± 8.6	89.8 ± 9.2	0.83
Slope (bpm/sec)	4.20 ± 0.62	4.12 ± 0.52	2.88 ± 0.54	0.068
TAD (bpm/sec)	123171 ± 6362	121889 ± 5740	113334 ± 6153	0.14

Values showed as mean ± standard error

Table 1: Comparison between markers and pH groups at each time point (from stability to last occlusion).

FHR = fetal heart rate, MAP = mean arterial pressure, RMSSD = root mean square of successive differences, SDNN = standard deviation of normal to normal R-R intervals, STV = short-term variation, LF = low frequencies, HF = high frequencies, HFnu = normalized high frequencies, FSI = fetal stress index, TAD = total area of deceleration

Table 2: Correlation between hemodynamic, HRV and characteristics of deceleration with pH, lactate and base excess at each time point (from stability to last occlusion)

	pH		Lactate		Base excess	
	$\beta \pm \text{SEM}$	P	$\beta \pm \text{SEM}$	P	$\beta \pm \text{SEM}$	P
FHR	-0.0007 ± 0.0004	0.063	0.009 ± 0.011	0.39	-0.0147 ± 0.019	0.45
MAP	-0.003 ± 0.001	0.006	0.079 ± 0.026	0.004	-0.110 ± 0.051	0.036
RMSSD	-0.001 ± 0.001	0.21	0.036 ± 0.026	0.17	-0.054 ± 0.041	0.19
SDNN	-0.001 ± 0.001	0.35	0.041 ± 0.032	0.20	-0.004 ± 0.060	0.95
STV	-0.001 ± 0.004	0.87	0.14 ± 0.11	0.21	0.29 ± 0.21	0.18
LF	-0.021 ± 0.032	0.51	0.798 ± 0.882	0.37	0.321 ± 1.756	0.86
HF	-0.024 ± 0.042	0.57	0.983 ± 1.132	0.39	-0.099 ± 2.290	0.97
HFnu	0.02 ± 0.10	0.83	0.086 ± 2.873	0.98	-4.57 ± 5.15	0.38
FSI	-0.003 ± 0.001	<0.001	0.056 ± 0.022	0.015	-0.065 ± 0.037	0.087
Amplitude	-0.0002 ± 0.0004	0.64	0.005 ± 0.008	0.52	0.016 ± 0.019	0.42
Slope	-0.010 ± 0.006	0.070	0.104 ± 0.119	0.39	-0.127 ± 0.311	0.69
TAD*	-0.007 ± 0.006	0.28	0.19 ± 0.16	0.24	0.34 ± 0.25	0.19

*for the increase of 10000 units of TAD.

FHR = fetal heart rate, MAP = mean arterial pressure, RMSSD = root mean square of successive differences, SDNN = standard deviation of normal to normal R-R intervals, STV = short-term variation, LF = low frequencies, HF = high frequencies, HFnu = normalized high frequencies, FSI = fetal stress index, TAD = total area of deceleration