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PAPER

Can fetal heart rate variability obtained from cardiotocography provide the same diagnostic value like from electrophysiological interbeat intervals?

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Abstract

Objective. Fetal heart rate variability (HRV) is widely used for monitoring fetal developmental disturbances. Only expensive fetal magnetocardiography (fMCG) allows the precise recording of the individual fetal heart beat intervals uncovering also highly frequent vagal modulation. In contrast, transabdominal fetal electrocardiography (fECG) suffers from noise overlaying the fetal cardiac signal. Cardiotocography (CTG) is the clinical method of choice, however, based on Doppler ultrasound, improper to resolve single beats concisely. The present work addresses the transferability of established electrophysiological HRV indices to CTG recordings during the fetal maturation period of 20–40 weeks of gestation (WGA). *Approach.* We compared (a) HRV indices obtained from fMCG, CTG and fECG of short-term amplitude fluctuations (sAMPs) and long-term amplitude fluctuations (lAMPs) and complexity, and (b) their diagnostic value for identifying maturational age, fetal growth restriction (FGR) and small for gestational age (SGA). We used the functional brain age score (fABAS) and categories of long- and short-term regulation and complexity. *Main results.* Integrating all substudies, we found: (a) indices related to long-term regulation, and with modified meaning and values of short-term regulation and sympathovagal balance (SVB) according to electrophysiological HRV standards can be obtained from CTG. (b) Models using HRV indices calculated from CTG allow the identification of maturational age and discriminate FGR from controls with almost similar precision as electrophysiological means. (c) A modified set of HRV parameters containing short- and long-term regulation and long-term/short-term ratio appeared to be most suitable to describe autonomic developmental state when CTG data is used. *Significance.* Whereas the predominantly vagally modulated beat-to-beat precise high frequencies of HRV are not assessable from CTG, we identified relevant

related HRV indices and categories for CTG recordings with diagnostic potential. They require further evaluation and confirmation with respect to any issues of fetal developmental and perinatal problems in subsequent studies. This methodology significantly extends the measures of established CTG devices.

Novelty and significance

HRV indices provide predestinated diagnostic markers of autonomic control in fetuses. However, the established CTG does not provide the temporal precision of electrophysiological recordings.

Beat-to-beat related, mainly vagally modulated behavior is not exactly represented in CTG. However, a set of CTG-specific HRV indices that are mainly comparable to established electrophysiological HRV parameters obtained by magnetocardiography or electrocardiography provided almost similar predictive value for fetal maturational age and were helpful in characterizing FGR.

These results require validation in the monitoring of further fetal developmental disturbances.

We recommend a corresponding extension of CTG methodology.

1. Introduction

Heart rate variability (HRV) indices provide established diagnostic and prognostic markers of the functional state of the autonomic nervous system (ANS) (TaskForce 1996). In monitoring the fetal development from about 20 weeks of gestation (WGA) onwards, heart rate recordings are routinely obtained by external cardiotocography (CTG), and more recently by transabdominal fetal electrocardiography (fECG) and fetal magnetocardiography (fMCG) at the research level. Each methodology has particular advantages and disadvantages. A link between CTG, fECG and fMCG would allow merging and complementary analyses, sharing results and study data bases, and consequently improve diagnostic accuracy and reduce costs. The different resolution and error rate, hence, practicability and comparability of the obtained HRV indices are subject of the present work.

This topic is of outstanding practical relevance due to the different quality, costs and availability of these recording technologies. Since none of the methodologies meets all clinical requirements, we herein search for equivalent and complementary capabilities with respect to HRV analysis. CTG cannot acquire the electrophysiological cardiac excitation process and suffers from periods of lost signal, but it is widely established and accepted in clinical routine. Transabdominal fECG is inexpensive and can simply be applied in clinical routine, but it suffers from low signal-to-noise ratio. fECG scalp electrodes are limited to intrapartual use. fMCG allows the almost artifact-free identification of the RR interval sequences over gestation, but it is too expensive and inconvenient for clinical routine. Other methodologies such as fetal phonocardiogram or ultrasound-based individual beat detection are still in immature stage of development and not included in this analysis.

The electrophysiological heart beat detection considers the electrical heart muscle activity that results from the autonomic control of the sinus node. According to the sampling rate of the recordings, fECG and fMCG precisely measure fast, mainly vagal modulation of the interbeat intervals. For example, a sampling rate of 1000 Hz allows the evaluation of HRV frequencies up to 500 Hz as recommended (Grimm *et al* 2003). Transabdominal fECG mainly fails between 28th and 32nd WGA when the fetus is almost completely covered and electrically insulated by the vernix caseosa. Furthermore, the small heart vector in growth restricted (FGR) fetuses effects the low signal-to-noise ratio. fMCG allows the stable beat detection from some 15–20 WGA onwards; however, this technology requires expensive SQUID systems in magnetically shielded chambers and is not affordable for clinical routine. Furthermore, the recording duration is limited to about 30 min because of the required stationary position of the mother e.g. Hoyer *et al* (2017).

In contrast, ultrasound Doppler measures the beat related pulsing movement of the heart. For the calculation of the beat intervals the correlation over time windows of 1.2 s containing 2–3 beat intervals, is used. CTG is the established clinical routine, but it suffers from a high rate of technically disturbed periods that have to be eliminated. The loss of the individual RR intervals is inherent of the CTG data acquisition technology and it is clear that cardiogenic arrhythmias cannot be identified. But the relevance of this limitation for the assessment of the autonomic heart rate modulations by means of HRV indices that base on normal sinus rhythm has not sufficiently been investigated for clinical routine.

Schiermeier *et al* (2007) and Seliger *et al* (2016) reported the loss of the high frequency HRV due to the low-pass characteristic of the CTG methodology compared to electrophysiological recordings using fMCG and synchronous transabdominal fECG. Goncalves *et al* compared synchronous ante/intrapartual direct fECG obtained by scalp electrodes with external CTG in several studies. They found strong correlations in time domain and complexity HRV indices, but weak or missing correlations in frequency domain HRV indices depending on the period of labor (Goncalves *et al* 2006). These HRV indices partly differ between the beat-to-beat signal and 4 Hz and 2 Hz resampled signals of fECG and CTG, respectively (Goncalves *et al* 2013b). The differences of conventional CTG analysis (STV, LTV, baseline, accelerations and decelerations) of the same fetal heart rate signals obtained with direct fECG (scalp electrode during labor) comparing different sampling modes and rates (beat-to-beat, 4 Hz resampled signal) did not provide significant differences (Goncalves *et al* 2015). With respect to the evaluation of the maturational age between 20 WGA and 40 WGA by means of the functional fetal autonomic brain age score (fABAS) we found a high agreement between the original fMCG and its CTG-equivalently preprocessed version resampled at 4 Hz. In contrast, the predictive value of models fitted to CTG equivalent heart rate traces from fMCG was reduced when applied to CTG data from another study center (Hoyer *et al* 2017). This result reflects both, the different data acquisition and preprocessing technology and the physiological difference between different study groups.

In figure 1 the methodological differences are illustrated concerning their frequency response characteristics. The upper part shows the low-pass characteristics of the convolution with a 1.2 s window. Accordingly, the main part of the power spectra of the electrophysiological (beat-to-beat) signals and their CTG conform preprocessed versions are maintained. However, higher frequencies (of more than about 0.7 Hz according to the frequency response curve) are suppressed by CTG methodology. David *et al* (2007) described rhythms in frequency bands up to 1.7 Hz by dynamic wavelet analysis that are typically smoothed in the conventional power spectral analysis. It should be noted that artifacts feign periods of increased variability and, therefore, erroneous power throughout the whole spectra. We aimed to select examples devoid of artifact as far as technically possible.

Previously, we proposed the autonomic functional brain age score (fABAS) to quantify the functional maturational age of the autonomic control based on universal principles of evolution and development (Hoyer *et al* 2013b). The independent age predicting value of the factors of this multivariate score was confirmed by an unsupervised selection procedure of HRV indices that was applied to 34 linear and 24 nonlinear HRV indices obtained from a set of 552 recordings of normal healthy fetuses (Schmidt *et al* 2018a, b). Subsequently, a small set of resulting HRV categories was proposed that contains predominant representatives of the myriad of redundant HRV indices in connection with the identification of several diagnostically relevant deviations of fetal autonomic tone (Hoyer *et al* 2019). The sympathovagal balance (SVB) is a further key feature of autonomic tone that was defined by the ratio of slow and fast autonomic rhythms (David *et al* 2007, Schneider *et al* 2009).

The present work addresses the questions, to which extent the loss of high frequencies in the modulation spectrum (indicator of vagal activity) alters HRV indices and their diagnostic value comparing CTG recordings and precise electrophysiological recordings (fMCG). In that respect, also fECG recordings were comprised. We considered representative indices of the HRV in categories, the fABAS, and SVB calculated from CTG, fECG and fMCG recordings. According to the limitations of synchronous recordings, we organized several related substudies.

HRV index couples of different technologies were compared according to availability between

- HRV indices based on fMCG recordings with their CTG-equivalently preprocessed versions.
- HRV indices of quasi synchronous transabdominal fECG and CTG recordings.
- HRV indices of subsequent fMCG and CTG recordings.

With respect to the evaluation of the maturational age we compared

- HRV indices based on fMCG recordings with their CTG-equivalently preprocessed versions.
- CTG based HRV indices with those of CTG-equivalently preprocessed fMCG.

With respect to the identification of pathological deviations we compare HRV indices:

- FGR vs. normal of fMCG and their CTG-equivalently preprocessed versions.
- FGR vs. normal from CTG recordings (similar study center).
- SGA vs. normal from CTG recordings (similar study center).

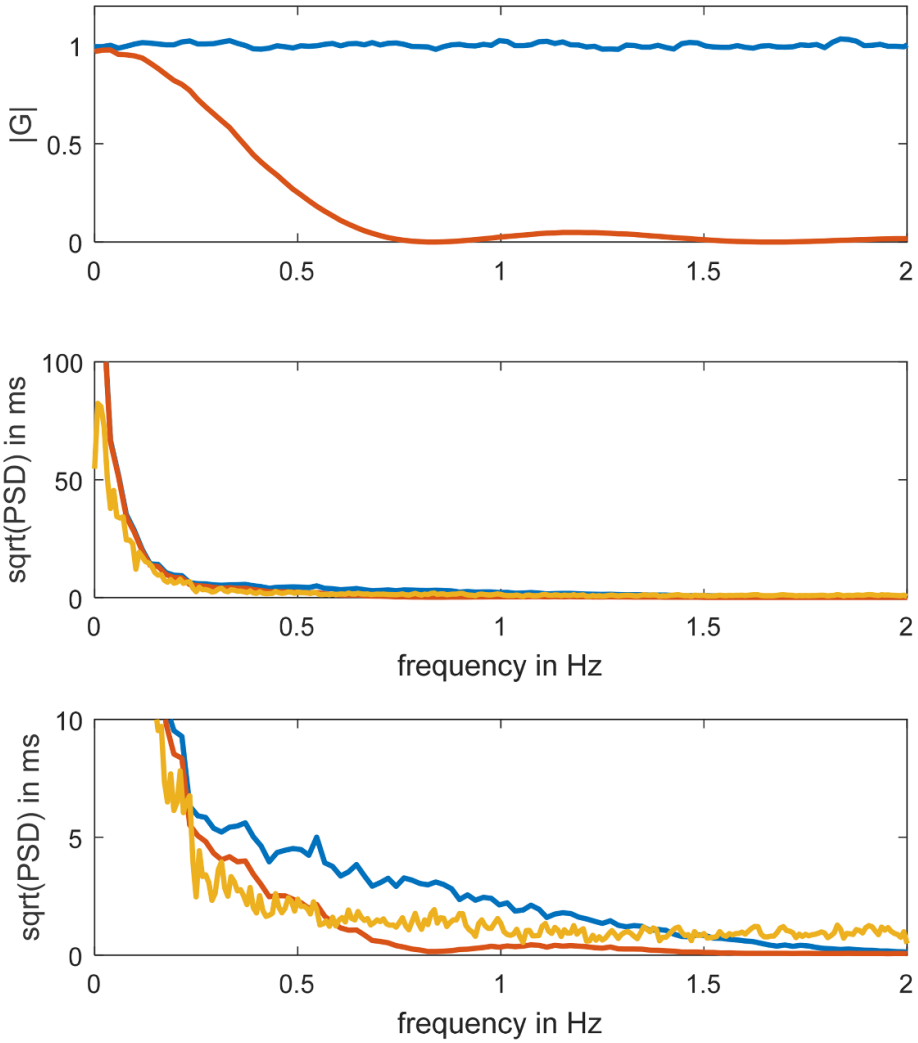

Figure 1. Frequency response of simulated white noise (blue) convoluted with 1.2 s window according to commercial CTG preprocessing (red) (upper part). Power spectra of fMCG recordings, average of three recordings in 2F (blue), of their CTG conform preprocessed versions (red), and of CTG recordings, average of three recordings in 2F (yellow) (middle part), zoomed section (bottom part).

2. Methods

2.1. Subjects and recordings

All recordings (see table 1) were approved by the respective local Ethics Committees and the mothers gave their informed consent. The recordings were performed as previously reported by fMCG (Jena) (Hoyer *et al* 2013b, 2017), CTG Porto (Amorim-Costa *et al* 2017, Goncalves *et al* 2018), CTG Munich (Lobmaier *et al* 2012), concurrent CTG and transabdominal fECG Munich (Lobmaier *et al* 2018). Table 1 gives an overview of the different data sets.

The CTG signals were used as available from the output of the commercial CTG monitors at 4 Hz.

Hewlett-Packard CTG monitors M1350A or M1351 (Philips Healthcare, DA Best, The Netherlands) were used in Porto and Munich (FGR vs. normal study), Sonicaid CTG monitors (Huntleigh Healthcare Limited/Oxford Instruments Medical Ltd Surrey, UK) in Jena and Munich (fECG vs. CTG study) CTG recordings. fMCG and fECG were sampled at 1024 Hz.

According to the different methodologies the average length of the recordings and their analyzable sections differed as follows:

fMCG:	30.1 ± 0 min	29.1 ± 4.3 (94.4%) min
fECG:	45.4 ± 7.6 min	33.4 ± 17.5 (73.7%) min
CTG (Munich):	55.2 ± 18.5 min	34.5 ± 15.5 (63.8%) min
CTG (Porto):	34.3 ± 9.9 min	26.1 ± 8.4 (76.9%) min

Table 1. Data sets: fMCG, CTG-equivalently resampled fMCG ($fMCG_{CTGequi}$), CTG, fECG.

Ci	Prediction/comparison	Group	Recording	Sample size	WGA range	Study center
1	fMCG vs. $fMCG_{CTGequi}$ (maturation age)	Normal	fMCG	620	20–40	Jena
		Normal	$fMCG_{CTGequi}$ (pairs)	620	20–40	Jena
2	$fMCG_{CTGequi}$ vs. CTG (maturation age)	Normal	$fMCG_{CTGequi}$	620	24–40	Jena
		Normal	CTG	333	24–41	Porto
3	fECG vs. CTG (quasi synchronous)	Normal	fECG	43	31–40	Munich
		Normal	CTG	43	31–40	Munich
4	fMCG vs. CTG (subsequent measures)	Unselected clin. cases	CTG	69	24–40	Jena
		Unselected clin. cases	fMCG (pairs)	69	24–40	Jena
		FGR, normal	fMCG	33 FGR 573 normal	24–39	Jena
5	fMCG vs. $fMCG_{CTGequi}$ (FGR vs. normal)	FGR, normal	$fMCG_{CTGequi}$	33 FGR 573 normal	24–39	Jena
6	CTG (FGR vs. normal)	Normal	CTG	36	26–38	Munich
		FGR	CTG	23	27–38	Munich
7	CTG (SGA vs. normal)	Normal	CTG	333 (50 subj.)	24–41	Porto
		SGA	CTG	79 (13 subj.)	24–40	Porto

In C1 and C5 indices the identical recordings were considered. In C2, C6, C7 different subjects were compared. In comparison C3 (quasi synchronous) fECG and CTG were recorded from the same subject at the same time. But due to the artifacts and dropouts appearing at different times in fECG and CTG the compared sections are not exactly identical. In C4 fMCG and CTG were subsequently recorded in the same subject at the same day.

Inclusion criteria were fetal heart rate recordings in sinus rhythm of singletons during the second and third trimester, maternal age >18 years.

Maternal exclusion criteria were known heart disease, medication affecting cardiac function, smoking, abuse of alcohol or illicit drugs and diabetes mellitus (preexisting and gestational). Fetal exclusion criteria were known chromosomal or other structural abnormalities, uterine contractions during recording, and cardiac arrhythmias.

Study groups:

- The normal group was defined by lack of any known pathologic disturbances according to the results of regular maternity care in the respective countries.
- Group of unselected clinical cases, obstetric inpatients: the collective is composed of obstetric inpatients. They were consecutively recruited based on assessment of acceptably low risk to perform the recording and voluntary consent. The patients were in the obstetric ward for miscellaneous reasons and served as their own controls when fMCG and CTG recordings were performed within an hour the same afternoon.
- FGR was assumed when the sonographically estimated fetal weight was observed below the 10th percentile in combination with (Jena) pathologic uteroplacental perfusion on Doppler ultrasound beyond 24 WGA (mean pulsatility index in the Aa. Uterinae >1.5 and/or bilateral notching) (Voigt *et al* 1996, Baschat *et al* 2000) or (Munich) an umbilical artery resistance index (RI UA) >95th percentile.
- SGA was defined by birth weight below the 10th percentile for gestational age (Hadlock *et al* 1991).

Three independent obstetricians at the Jena study center classified the fetal behavioral states by visual inspection of the heart rate pattern printout after a consensus decision (Nijhuis *et al* 1982, Schneider *et al* 2009, Hoyer *et al* 2013a). Only periods of active sleep (2F) were analyzed according to CTG recommendations (FIGO 2011).

2.2. Simulation of CTG preprocessing

The CTG typical signal acquisition and preprocessing was simulated in fMCG data by means of a 4 Hz resampling of the RR series and a moving average window over 1.25 s (five re-samples) according to the correlation window length used in all CTG devises (1.2 s).

Table 2. HRV indices, overview, for details see Hoyer *et al* (2019) extended by SVB category.

		HRV index	Meaning
Categories	sAMP	pNN5 | pNN5 (CTG)	Percentage of differences between adjacent NN intervals exceeding 5 ms | between adjacent CTG samples
		ACst1 | ACst1 (CTG)	Acceleration Capacity index, step value over adjacent NN intervals | CTG samples
	lAMP	AMP20tr | AMP20tr (CTG)	Amplitude range: 20–95 interquantile distance of detrended NN interval series | CTG samples
		STVms	Short-term variability according to CTG calculation procedure
		LZC | LZC (CTG)	Lempel Ziv complexity of binary transformed NN intervals | CTG samples
	Short-term complexity (sCOMP)	MSE1 | MSE1 (CTG)	Generalized multiscale entropy at coarse graining level 1, adjacent NN intervals | adjacent CTG samples (only reported when LZC n.s.)
	Long-term complexity (lCOMP)	MSE4 (NN) | MSE7 (CTG)	Generalized multiscale entropy at coarse graining level (4 adjacent NN intervals averaged) | (7 adjacent CTG samples averaged)
	Patterns	Skewness	Skewness of NN intervals | CTG samples
fABAS	Functional fABAS	(AMP, MSE3, skewness, pNN5,VLF/LF)	Linear regression model that enters these HRV indices
Category	SVB	VLF/LF	Quotient of very low (0.02–0.08 Hz) and low (0.08–0.2 Hz) frequency band power
		VLF/HF	Quotient of very low frequency and high frequency (0.4–1.7 Hz) band power
		SDNN/RMSSD | SDNN/RMSSD (CTG)	Quotient of total fluctuations and fast fluctuations of NN intervals | CTG samples

2.3. HRV indices

We included proxy HRV indices according to previously proposed HRV categories (Hoyer *et al* 2019), the functional fABAS (Hoyer *et al* 2013b), and indices related to SVB (David *et al* 2007, Schneider *et al* 2009). The Acceleration Capacity index (ACst1) estimates the average value of all increases of subsequent beat-to-beat heart rate values or subsequent samples, respectively, and belongs to the short-term indices. It was motivated by the phase-rectified signal averaging methodology that considered the increase between the averages of 10 s windows before and after anchor points, as appropriate to identify FGR fetuses (Lobmaier *et al* 2012) and belongs to the long-term categories according to the present classification. Furthermore should be noticed that the STV (known as 'short-term variation' with a temporal resolution of 16×3.75 s $= 1$ min (Pardey *et al* 2002) belongs to the long-term indices and does not consider the fast, beat-to-beat mediated vagal heart rate modulations.

Electrophysiological recordings of NN interval series are the source of the original indices as outlined in table 2. The CTG specific indices were obtained from time series sampled at 4 Hz device-internal calculated from a 1.2 s correlation window. Therefore, the identical annotation relates to in parts deviant statistics. With respect to the established HRV annotations and our intention of its equivalent readability from CTG, we waived the attempt to replace NN (normal-to-normal) by samples for CTG and CTG-equivalently preprocessed data. Finally, we added the attribute CTG where samples were used. In spite of the NN intervals, the samples every 250 ms were used in the formally identical calculation functions. STV of NN intervals and power spectral parameters use equivalent resampling, and hence do not need the CTG attribute.

Artifact correction was done as follows. At the beginning the signal was broken down into 1 min segments. Each segment was checked for heart rate (HR) values outside the range of 100–200 bpm and absolute values of the difference between consecutive heart beats | samples exceeding 10 bpm. Segments containing more than 10% (fMCG) or 20% (fECG, CTG) outliers were removed. The remaining signal parts with a length of at least 5 min were scanned for outliers using the same criteria as mentioned above. If an outlier was detected a section with stable fetal HR was searched for. A section was considered to be stable if the criteria were not violated over five adjacent heart beats (fECG/fMCG) or 3 s (CTG). The disturbed sections were spline interpolated. Furthermore, the automatic artifact correction results were visually controlled and, if necessary, missed outliers were manually removed. In fMCG data, signal parts with up to 5% artifacts were accepted. In CTG and fECG data we increased the threshold to 10% due to the lower signal-to-noise ratio in order to reduce the number of recording dropouts. Based on the resulting artifact-corrected signals, the HRV parameters were calculated using a 5 min window shifted by 1 min steps.

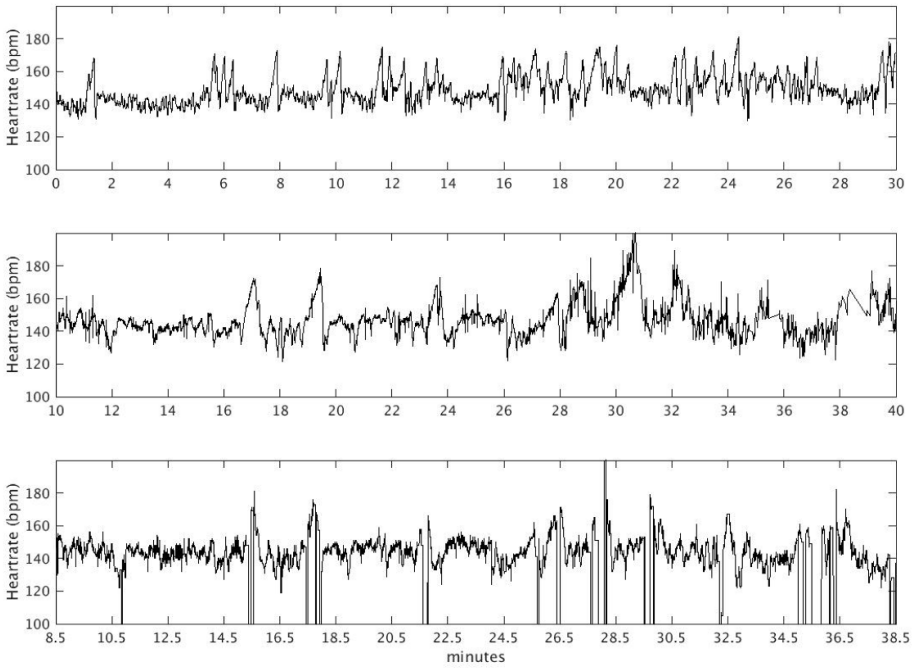

Figure 2. Examples of typical heart rate traces from fMCG (top), fECG (center) and CTG (bottom) in active sleep. Note the effects of spurious beat detections (needles) in fECG and dropout periods in CTG.

Finally, the HRV parameters were weighted averaged according to the length of the considered signal parts of the respective recording.

2.4. Statistics

The agreement between the recording methods of HRV indices was presented by Bland–Altman plots, namely their differences (mean ± 1.96 SD) versus their mean values (Bland and Altman 1986). The weight of the differences was quantified by the diff/mean range ratios (DMRR), estimated by ±1.96 SD range of the differences/±1.96 SD range of the mean values of the HRV index couples. Concerning the random error a reasonable transferability requires a range of differences that is clearly smaller than the range of mean values.

Reasonable individual couples were HRV indices from (a) fMCG with CTG-equivalently preprocessed fMCG, (b) fECG with CTG, (c) fMCG with CTG.

Dependencies on fetal maturational age were estimated for HRV indices including fABAS by linear regression models, quantified by their standardized regression coefficient (beta), coefficient of determination (R^2) and standard error (SE). Models with $R^2 < 0.1$ were considered as irrelevant and marked by n.s. even when $p < 0.05$. The best predicting multivariate regression models were built by stepwise forward procedure.

Group differences were investigated by binary logistic regression models containing the main factors (HRV index, WGA) and their interaction. Area under curve (AUC) with 95% confidence interval (CI) of receiver operator characteristic (ROC) curves was reported. Different sample sizes were balanced by weighted cases. In case of repeated measures the intra-individual dependencies were considered by corresponding generalized estimation equation regression models (comparisons 6 and 7). Since found irrelevant in pre-analyses of the fMCG dataset, intra-individual dependencies of repeated measures were ignored in comparisons 1 and 2.

The WGA range was considered according to the overlapping range of the particular comparison.

Bivariate correlations among HRV parameters were given by the Pearson correlation coefficient r.

$P < 0.05$ was considered significant. Non-significant results were marked by n.s.

3. Results

Figure 2 depicts examples of typical heart rate traces from fMCG, fECG and CTG recordings in active sleep 2F. They demonstrate the different signal quality like almost perfect fMCG beat detection using fMCG, partly disturbed beat detection using fECG beat detection and some dropout periods using CTG acquisition.

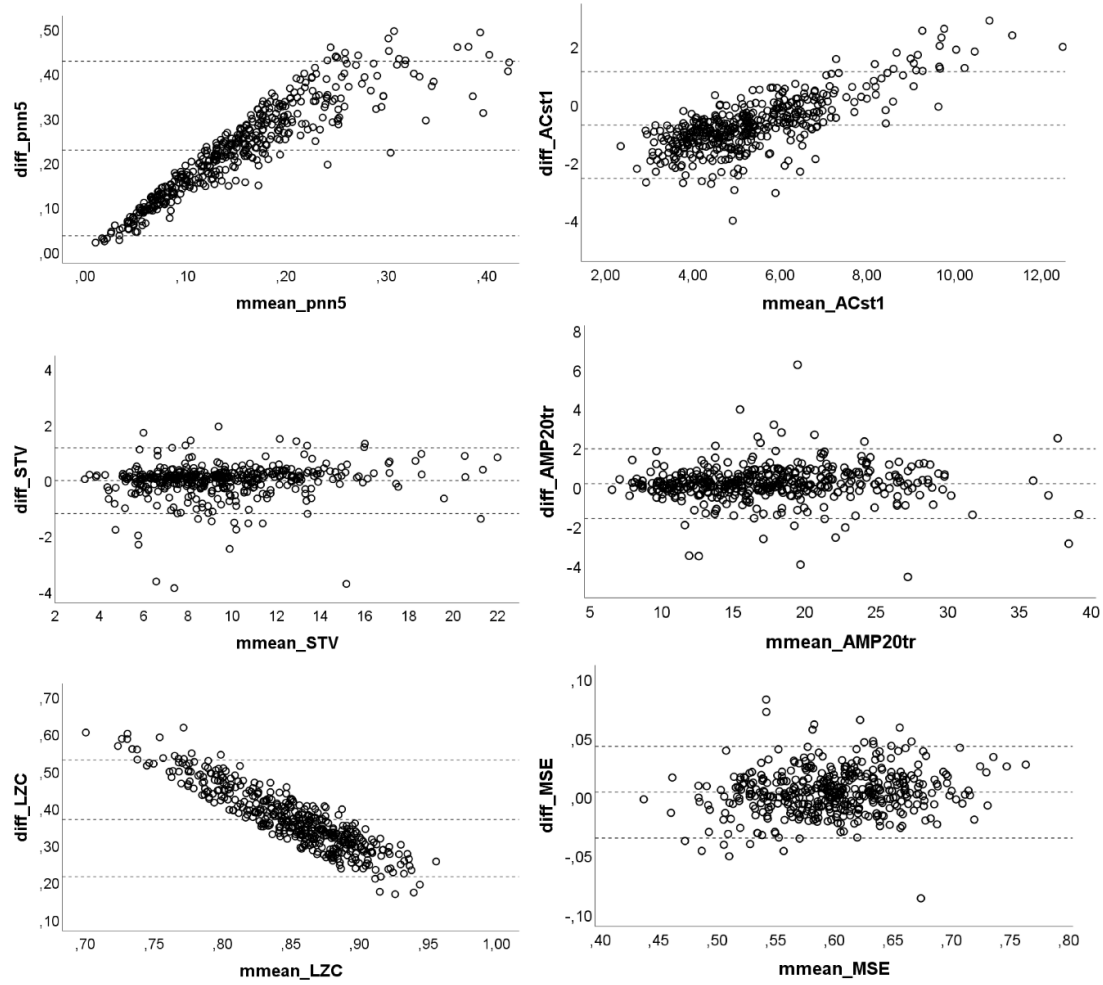

Figure 3. Comparison 1: Bland–Altman plots of HRV parameters according to fMCG and their CTG-equivalent preprocessing, mean ± 1.96 SD. The long-term parameters (STV, AMP20tr) show mainly agreement. MSE of comparable scales, namely MSE4 (fMCG, four beat intervals)—MSE7 (CTG, 7 × 0.25 s) show a lower level of agreement. The plots of the other parameters may suggest systematic relationships.

3.1. Comparison1: fMCG vs. $fMCG_{CTGequi}$ (normal, individual pairs, maturation age)

The Bland–Altman plots (figure 3) show a reasonable agreement of the lAMP indices with DMRR values of 2.3/12.5 = 0.19 for STV and 3.6/22.3 = 0.16 for AMP20tr. In contrast, the sAMP indices show systematic increases of the differences, leading to DMRR values of 0.39/0.31 = 1.25 in pNN5 and to lower extend of 3.7/6.2 = 0.59 in ACst1. Correspondingly, the sCOMP values were altered more substantially than the lCOMP values, namely 0.31/0.18 = 1.78 (LZC) vs. 0.08/0.21 = 0.37 (MSE). The systematic increases of pNN5 differences over the increasing mean values reflect the increasing suppression of the CTG equivalent indices with increasing amplitude, which is associated with increasing frequency. The same phenomenon, but less clear, appears for the ACst1 differences. These results are consistent with the loss of heart beat related information in the equidistant heart rate time series obtained by a correlation window.

The resulting question is whether relevant short-term characteristics maintain the systematic suppression of fast frequencies. The correlations between indices obtained from NN and CTG-equivalently preprocessed versions show remaining strong correlations within the long-term indices. The short-term index pNN5 was only a little less correlated. ACst1 exhibits a partially different behavior (table 3(a)). The remarkable correlations between the short- and long-term indices (table 3(b)) superimpose this signal processing aspect.

With respect to the maturational age models (table 4), the CTG equivalent preprocessing of fMCG changed the predictive value only to some regard. The short-term index pNN5 and ACst1 lost a part of their predictive value. The other indices performed mainly similar in both data sets. The partly improvement of skewness might be consistent with a previous analysis that suggested better identification of long-term

Table 3(a). Correlations r between AMP indices from NN (fMCG) and their CTG-equivalently preprocessed versions (Jena).

RES/NN	pNN5	ACst1	AMP20tr	STVms
pNN5 (CTG)	0.67	0.87	0.62	0.78
ACst1 (CTG)	0.63	0.90	0.58	0.84
AMP20tr (CTG)	0.60	0.68	0.98	0.76
STVms	0.73	0.90	0.74	0.98

Table 3(b). Correlations between the AMP indices obtained from NN data.

NN/NN	pNN5	ACst1	AMP20tr	STVms
pNN5	1	0.74	0.62	0.74
ACst1		1	0.69	0.90
AMP20tr			1	0.73
STVms				1

Table 4. Maturation age predicting value (R^2, SE) of HRV indices obtained from on fMCG recordings in comparison to their CTG-equivalently preprocessed versions (identical recordings).

Table 4 (comparison1)		fMCG (NN)			fMCG (CTGequivalent)		
HRV		Beta	R^2	SE	Beta	R^2	SE
sAMP	pNN5 | pNN5(CTG)	0.58	0.34	3.78	0.28	0.08	4.48
sAMP	ACst1 | ACst1(CTG)	0.50	0.25	4.03	0.47	0.22	4.12
lAMP	AMP20tr | AMP20tr(CTG)	0.61	0.37	3.70	0.58	0.33	3.81
lAMP	STVms	0.53	0.28	3.93	0.51	0.26	4.01
sCOMP	LZC | LZC(CTG)		n.s.			n.s.	
lCOMP	MSE4(NN) | MSE7(CTG)[a]	0.42	0.17	4.22	0.42	0.18	4.22
Pattern	Skewness | Skewness(CTG)	0.51	0.26	3.99	0.59	0.34	3.78
Pattern	VLF/LF		n.s.			n.s.	
fABAS			0.52	3.23		0.54	3.17

[a]Approximately similar time scales are 4 mean heart rate intervals (4 × 426 ms = 1.704 s) vs. 7 CTG samples (=1.75 s).

Table 5. Age predicting value (R^2, SE) of HRV indices obtained from CTG recordings vs. those from fMCG (different study centers, Jena-Porto).

Table 5 (comparison2)		$fMCG_{CTGequi}$			CTG Porto		
HRV		Beta	R^2	SE	Beta	R^2	SE
sAMP	pNN5 (CTG)	0.26	0.07	3.93	0.47	0.21	3.81
sAMP	ACst1 (CTG)	0.41	0.19	3.71	0.38	0.14	3.98
lAMP	AMP20tr (CTG)	0.54	0.29	3.41	0.45	0.20	3.84
lAMP	STVms	0.43	0.19	3.67	0.58	0.10	4.09
sCOMP	LZC (CTG)		n.s.			n.s.	
lCOMP	MSE7 (CTG)	0.34	0.11	3.83	0.34	0.11	4.04
Pattern	Skewness (CTG)	0.57	0.33	3.34	0.55	0.30	3.60
Pattern	VLF/LF		n.s.			n.s.	
fABAS			0.47	3.00		0.45	3.18

autonomic controllers on time base than on beat interval base (Hoyer *et al* 2011). The multivariate fABAS model best predicted the physiological maturational age as expected.

3.2. Comparison2: $fMCG_{CTGequi}$ vs. CTG (normal, maturation age)

The present comparison addresses both, the differences between the populations of the study centers as well as signal acquisition and quality aspects. In both signals the separately fitted fABAS clearly best represented the autonomic maturation age (table 5). The differences do not suggest a clear systematic advantage of one of the signals.

3.3. Comparison3: fECG vs. CTG (normal, quasi synchronous pairs)

This comparison included the different signal base (fECG NN vs. CTG) of synchronous recordings (Munich), however separately considered artifact free sections. The Bland–Altman plots and DMRR values around one indicate a low level of equality (figure 4). Tendencies similar to fMCG vs. fMCG (figure 3) are the systematic increase of pNN5 and decease of LZC. As expected were the lacking agreement of the short-term

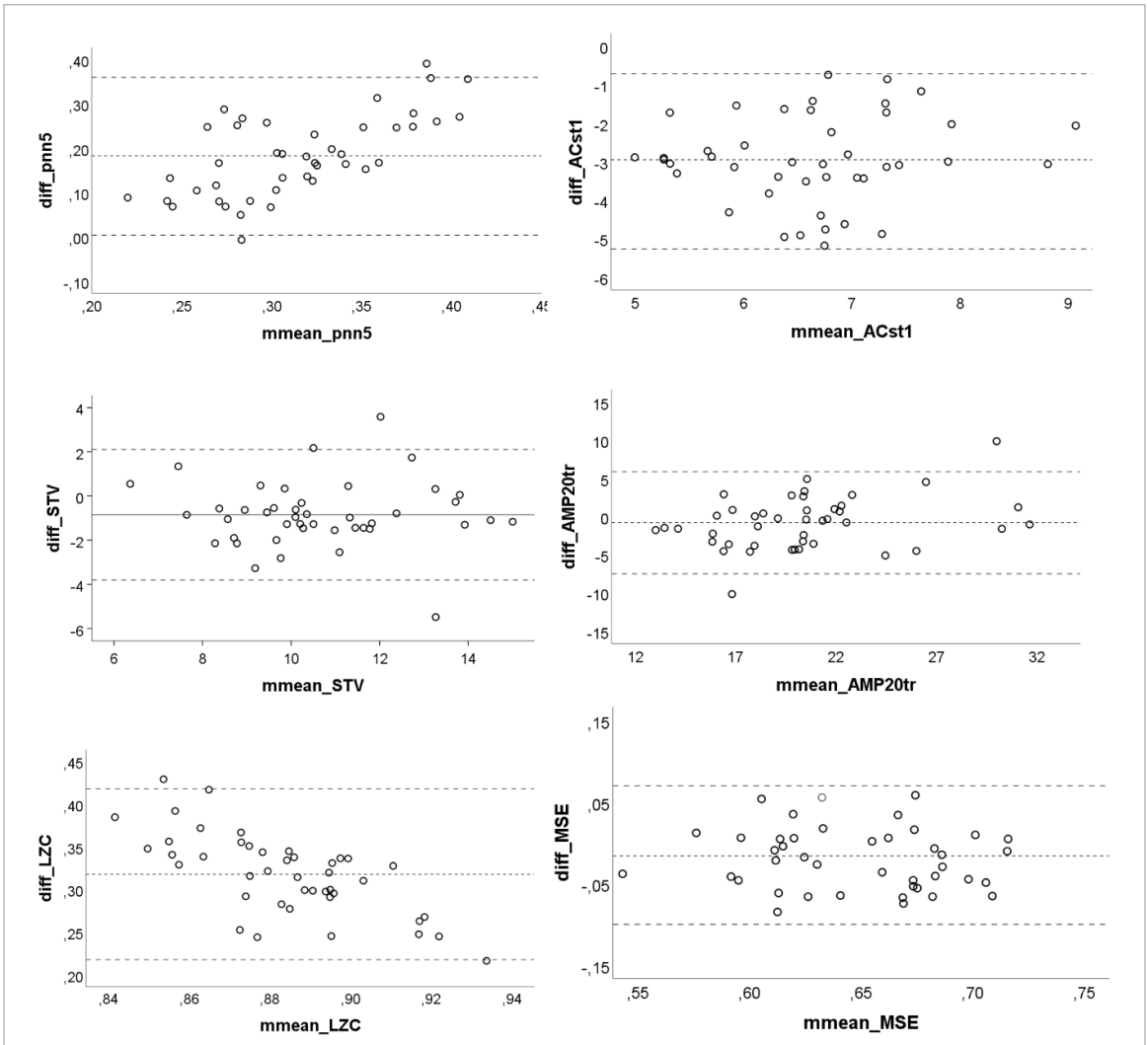

Figure 4. Comparison 3: Bland–Altman plots, fECG vs. CTG, the DMRR are 5.84/7.80 = 0.75 (STV), 13.48/17.52 = 0.77 (AMP20tr), 0.35/0.20 = 1.8 (pNN5), 4.5/3.5 = 1.29 (ACst1), 0.20/0.08 = 2.5 (LZC), 0.17/0.17 = 1 (MSE).

index pNN5 with DMRR = 1.8(0.35/0.20) and the best agreement for the long-term index AMP20tr with DMRR = 0.77(13.48/17.52). These values of low agreement also reflect the overall lower rates of artifact free parts in fECG (73.7%) and CTG (60.1%) in comparison to fMCG (94.4%) (table 1).

3.4. Comparison4: CTG vs. fMCG (unselected clinical cases, pairs of immediate repeat measurers)

This comparison addresses the reproducibility of the repeated measures (similar patient on the same day) and the difference between the recording technologies. In order to evaluate the transferability of discriminatory values of indices, we dichotomized the fMCG data for each HRV index separately. Subsequently, we discriminated these groups with respect the corresponding HRV index of the subsequent repeat CTG recordings.

In the Bland–Altman plots the best DMRR values of about 1 for lAMP indicate an error range at the level of the variance of this heterogeneous population (figure 5). Nevertheless, the discriminatory value of the CTG data show significant discriminatory power that suggest a maintenance of fMCG median split based assignment in lAMP indices as expected, but surprisingly also in pNN5. The latter result can be explained by an appropriate consideration of the systematic increase of pNN5 as shown in figure 3. From the indices of SVB maintained the fMCG generated assignment in SDNN/RMSSD and by tendency in VLF/LF (figure 6, table 6).

3.5. Comparison5: fMCG vs. $fMCG_{CTGequi}$ (FGR vs. normal, pairs of identical recordings)

The comparison of the discrimination result (FGR vs. healthy controls) between NN interval series and their CTG-equivalently preprocessed heart rate time series addresses the influence of preprocessing according to this mode of data acquisition technology. Since using identical recordings any influences by different artifact rate or study populations are excluded.

Table 6. Results of ROC analysis of HRV calculated from CTG recordings (Jena) with respect to dichotomized fMCG indices of the preceding fMCG recording of the identical subjects (Jena); see also figures 5 and 6.

Table 6

HRV (adjusted for GA)		ROC characteristics AUC (95% CI)
sAMP	pNN5(CTG)	0.74 (0.62, 0.86)
sAMP	ACst1(CTG)	0.62 (0.49, 0.76) n.s.
lAMP	AMP20tr(CTG)	0.75 (0.63, 0.87)
lAMP	STVms	0.76 (0.64, 0.87)
sCOMP	LZC(CTG)	0.48 (0.34, 0.62) n.s.
lCOMP	MSE7(CTG)	0.56 (0.42, 0.70) n.s.
SVB	VLF/LF	0.63 (0.50, 0.77) n.s.
SVB	VLF/HF	0.62 (0.48, 0.75) n.s.
SVB	SDNN/RMSSD(CTG)	0.65 (0.51, 0.78)

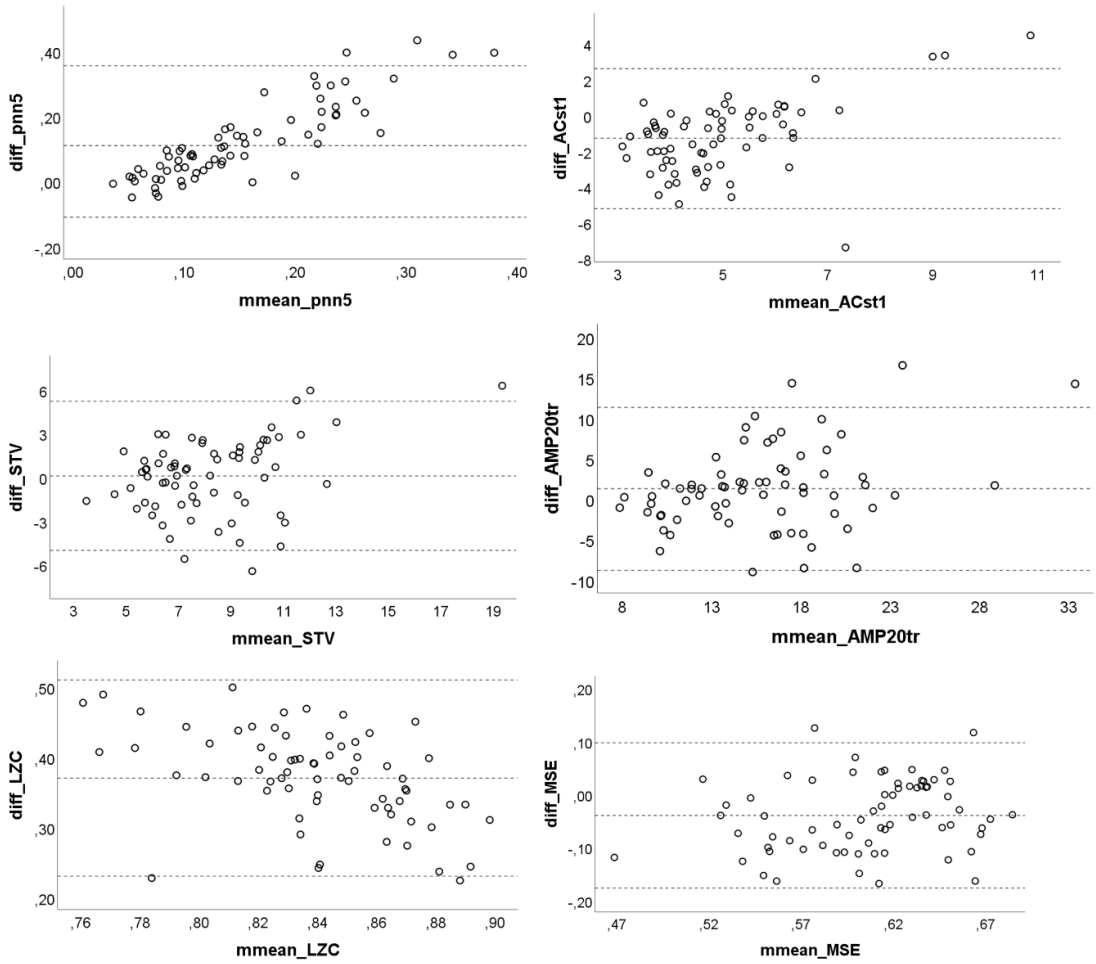

Figure 5. Comparison 4: Bland–Altman plots, fMCG vs. CTG, the DMRR are 10.2/9.8 = 1.03 (STV), 20.2/18.5 = 1.09 (AMP20tr), 0.47/0.31 = 1.5 (pNN5), 7.8/5.5 = 1.43 (ACst1), 0.27/0.16 = 2.33 (LZC), 0.27/0.16 = 1.75 (MSE).

We found similar discriminatory value of almost all HRV indices. In both signal modes ACst1 and STV, as representatives of short- and long-term fluctuation amplitude, best discriminated FGR from healthy controls in the univariate analysis. All indices of SVB significantly discriminated in both data modes. The parameter sets of the best discriminating models confirm the relevance of sAMPs and lAMPs, SVB, and sCOMP. The multivariate models provided similar discriminatory value in NN and CTG-equivalently preprocessed fMCG data (table 7).

3.6. Comparison6: CTG (FGR vs. normal)

This comparison addresses the discriminatory value of the HRV indices and scores of CTG recordings between FGR and healthy controls (both Munich, table 8). Useful for comparison fMCG results obtained from another study population (Jena) are shown in table 7.

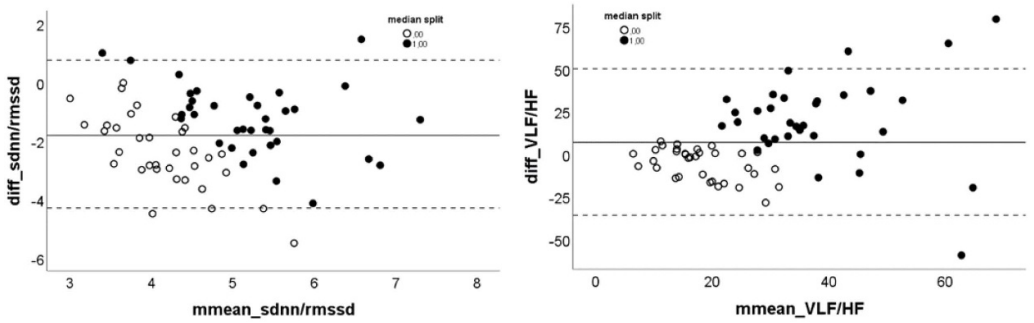

Figure 6. Comparison 4: Bland–Altman plots, fMCG vs. CTG, of SVB, the DMRR are 5.1/3.5 = 1.44(SDNN/RMSSD) and 86/55 = 1.57 (VLF/HF). In contrast to the perfect discrimination of median split fMCG data, the discriminatory ROC value in the CTG data are significantly reduced: AUC(SDNN/RMSSD) = 0.65(0.51,0.78), AUC(VLF/HF) = 0.62(0.48,0.75).

Table 7. Results of ROC analysis of HRV calculated from fMCG recordings (Jena) in comparison to their CTG-equivalently preprocessed versions (identical recordings), discrimination between FGA and normal fetuses.

Table 7 (comparison5)		ROC characteristics AUC (95% CI)	
HRV indices and models adjusted for GA		fMCG (NN)	$fMCG_{CTGequi}$
sAMP	pNN5 | pNN5 (CTG)	0.64 (0.61, 0.68)	0.66 (0.63, 0.69)
sAMP	ACst1 | ACst1 (CTG)	0.74 (0.71, 0.77)	0.75 (0.72, 0.78)
lAMP	AMP20tr | AMP20tr (CTG)	0.69 (0.66, 0.73)	0.65 (0.62, 0.69)
lAMP	STVms	0.78 (0.75, 0.81)	0.77 (0.74, 0.80)
sCOMP	LZC | LZC (CTG)	0.69 (0.66, 0.72)	0.70 (0.67, 0.73)
lCOMP	MSE4 | MSE7 (CTG)	0.64 (0.61, 0.67)	0.61 (0.58, 0.64)
Pattern	Skewness | Skewness (CTG)	0.63 (0.60, 0.66)	0.65 (0.62, 0.68)
fABAS | fABAS (CTG)		0.69 (0.66, 0.72)	0.69 (0.66, 0.72)
SVB	VLF/LF	0.59 (0.56, 0.62)	0.60 (0.57, 0.64)
SVB	VLF/HF	0.65 (0.61, 0.68)	0.65 (0.62, 0.68)
SVB	SDNN/RMSSD | SDNN/RMSSD(CTG)	0.62 (0.58, 0.65)	0.59 (0.56, 0.63)
Best discriminating models:		mHR, STV, MSE1: 0.80 (0.77, 0.83)	ACst1(CTG), STVms, pNN5(CTG),
		STVms, MSE1, SDNN/RMSSD: 0.80 (0.77, 0.83)	skewness(CTG), LZC(CTG): 0.81 (0.78, 0.83)

Table 8. Results of ROC analysis of HRV calculated from CTG recordings (Munich) for FGR and normal fetuses.

Table 8 (comparison5)		
HRV (adjusted for GA)		ROC characteristics AUC (95% CI)
sAMP	pNN5(CTG)	0.82 (0.72, 0.92)
sAMP	ACst1(CTG)	0.77 (0.66, 0.88)
lAMP	AMP20tr(CTG)	0.77 (0.66, 0.88)
lAMP	STVms	0.84 (0.74, 0.93)
sCOMP	LZC(CTG)	0.82 (0.72, 0.92)
sCOMP	MSE1(CTG)	0.61 (0.47, 0.74) n.s.
lCOMP	MSE7(CTG)	0.57 (0.43, 0.71) n.s.
Pattern	Skewness(CTG)	0.61 (0.48, 0.75) n.s.
fABAS		0.68 (0.56, 0.81)
SVB	VLF/LF	0.56 (0.42, 0.70) n.s.
SVB	VLF/HF	0.61 (0.48, 0.75) n.s.
SVB	SDNN/RMSSD(CTG)	0.60 (0.47, 0.74) n.s.
Best discriminating models:		
STVms, ACst1(CTG), VLF/HF:		0.89 (0.81, 0.96)
LZC(CTG), MSE1(CTG):		0.89 (0.82, 0.97)

All indices of sAMPs and lAMPs and one of sCOMP (LZC) discriminated FGR from normal. The best predicting single indices belong to sAMP and lAMP as correspondingly shown on fMCG data. The high predictive value of pNN5 reflects the amplitude differences of subsequent 4 Hz samples of the correlation based fetal heart rate signal. The indices of SVB did not discriminate the groups in contrast to those of the fMCG data shown in table 7. The best discriminating models included one of the best discriminating

Table 9. Results of ROC analysis of HRV calculated from CTG recordings (Porto) for SGA and normal fetuses.

Comparison 7		
HRV (adjusted for GA)		ROC characteristics AUC (95% CI)
sAMP	pNN5(CTG)	0.59 (0.54, 0.63)
sAMP	ACst1(CTG)	0.65 (0.60, 0.69)
lAMP	AMP20tr(CTG)	0.63 (0.59, 0.67)
lAMP	STVms	0.61 (0.57, 0.65)
sCOMP	LZC(CTG)	0.56 (0.52, 0.61)
sCOMP	MSE1(CTG)	0.64 (0.60, 0.68)
lCOMP	MSE7(CTG)	0.54 (0.50, 0.58) n.s.
Pattern	Skewness(CTG)	0.53 (0.49, 0.58) n.s.
fABAS		0.55 (0.50, 0.59)
SVB	VLF/LF	0.55 (0.51, 0.59)
SVB	VLF/HF	0.55 (0.50, 0.59)
SVB	SDNN/RMSSD(CTG)	0.58 (0.53, 0.62)
Best discriminating models:		
VLF/HF, SDNN(CTG), MSE1(CTG)		0.71 (0.67, 0.75)
ACst1(CTG), MSE1(CTG), MSE7(CTG)		0.69 (0.65, 0.73)

univariate indices (STVms or LZC). These models may be influenced by the unavoidable model selection problem of correlated factors (table 8).

3.7. Comparison7: discrimination of SGA from normal using CTG

This comparison addresses the discriminatory value of the HRV indices and scores in CTG recordings with regard to SGA versus normal (both Porto).

The SGA fetuses were best discriminated from normal fetuses by short and long-term indices of amplitude fluctuations and by sCOMP. The best discriminating models confirm the importance of the short- and long-term amplitude fluctuation, complexity and SVB. Please remember that these short-term characteristics describe the shortest part of the CTG inherent low passed filtered heart rate pattern (table 9).

4. Discussion

The fetal autonomic tone assessed by HRV characteristics has diagnostic potential that is not yet sufficiently explored for clinical routine. In that connection the evaluation of capabilities and limitations of CTG in comparison to electrophysiological recordings is an outstanding objective. We compared the diagnostic value of selected HRV indices obtained from fMCG, CTG-equivalently preprocessed fMCG, CTG and transabdominal fECG data sets. The different study centers obtained data sets according to the monitoring modalities available at each site and we performed overarching analyses according to the technical limitations of synchronous recordings and availability. We considered healthy populations and FGR/SGA fetuses as the first patient example to evaluate a clinically discriminatory value. Therefore, the present results may only give some indications and further studies are required to verify their value with respect to different clinical entities. fMCG served as reference standard since it is the most proficient technology of recording the cardiac trace with a minimum of artifacts.

The main findings integrating the comparisons C1–C7 are: (1) In contrast to the established long-term HRV indices, short-term and SVB indices are not equivalently obtainable from CTG (Bland–Altman plots); but (2) similarly calculated corresponding HRV indices provide a CTG specific set of HRV indices that allow the identification of maturational age and discrimination of FGR with almost similar precision as on fMCG (regression models).

C1: CTG equivalent preprocessing of fMCG data maintains the long-term HRV indices better than the short-term HRV indices. The transition from RR interval to CTG time series alters the original pulse-related information. However, there are remarkable correlations between all HRV indices.

C2: CTG-equivalently preprocessed fMCG data and CTG data are essentially equivalent.

C3: Transabdominal fECG and CTG based HRV indices seem to be more dispersed than those of fMCG due to their higher rate of technically disturbed parts.

C4: Intra-individual comparison of fMCG and consecutive CTG revealed only STV and lAMP to directly correspond between the two entities. The dichotomizations with respect to each index obtained from fMCG recordings were maintained in SDNN/RMSSD, STV, AMP20tr and pNN5 in CTG.

C5: The discrimination of FGR from healthy controls using fMCG recordings was not altered by CTG equivalent preprocessing of fMCG data. Indices of short-term, long-term and SVB (short-term/long-term ratio) statistically independently contributed.

C6: Indices of SVB lost their significance in the discrimination of FGR from healthy controls using CTG recordings (in comparison to fMCG, C5). Nevertheless, the models included indices of short-term, long-term and SVB (short-term/long-term ratio).

C7: The discrimination of SGA from normal fetuses using CTG recordings showed mainly similar characteristics like for FGR (C6), however with lower precision.

When ultrasound sensors are used in CTG devices, fetal heart rate values are obtained from the autocorrelation function of the fetal heart movement signal. In autocorrelation, a sliding window of 1.2 s is generally shifted across the signal and the average heart rate values obtained from these windows are stored in a buffer and read out four times per second (every 250 ms, 4 Hz) (Signorini *et al* 2003, Fanelli *et al* 2013). Established routine CTG characteristics are baseline heart rate, accelerations, and decelerations. Periodic rhythms, STV and LTV as calculated by the Dawes Redman algorithm include the elimination of disturbed sections but higher frequencies were methodically ignored (Pardey *et al* 2002). Both, STV and LTV, belong to the long-term HRV categories. In contrast to the HRV standards of adults, David *et al* (2007) described different band power ranges in fetuses, referred to as very low frequency (VLF) (0.02–0.08 Hz), low frequency (LF) (0.08–0.2 Hz) and high frequency (HF) (0.4–1.7 Hz) based on transabdominal fECG recordings. Both, LF and HF contain vagal, while VLF mainly sympathetic components. The authors proposed VLF/LF as possible component of SVB, but also VLF/HF and SDNN/RMSSD (Schneider *et al* 2009) are predestinated, in particular with regard to the fast vagal effects on the interbeat intervals. Van Leeuwen *et al* described an increasing HF range between 0.6 and 1 Hz as important for the fetal development of vagal control in fMCG recordings (2003). It corresponds to the appearance of rhythmic thoracic excursions that could be observed on ultrasound. Goncalves *et al* proposed frequency bands of VLF (0–0.03 Hz), LF (0.03–0.15 Hz), movement frequency (0.15–0.50 Hz) and HF (0.50–1.00 Hz) for the identification of severe intrauterine growth-restricted fetuses (2013a).

The results suggest that the main limitations of CTG, namely the loss of individual heart beat intervals in the 1.2 s autocorrelation of the ultrasound signal and the remarkable artifact/outage rate in contrast to exact electrophysiological heart beat intervals, may affect the clinical routine with respect to the characterization of maturation age and FGR on a minor extent only. Our results imply to define CTG specific HRV indices following the same scheme like the fECG/fMCG category set. The HRV indices of the long-term categories calculated from CTG signal can mainly be considered as similar to those calculated from fECG/fMCG. In contrast, the short-term category in CTG for the described reasons is not identical to those from electrophysiological methods. They reflect the fastest signal component of CTG, which results in different values when compared to fECG/fMCG. This difference could be indicated by the extension '(CTG)' for HRV indices of short-term and SVB obtained from the exported CTG traces and the CTG-equivalently preprocessed fMCG/fECG.

We elaborated statistically independent discriminatory values of long-term, short-term and SVB indices in fMCG data with respect to FGR. The same applies for the CTG data. Therefore, we propose to establish the previously defined HRV categories (Hoyer *et al* 2019) as an universal tool for fMCG/fECG and CTG. In that connection, we furthermore propose to extent this tool by a category of the important physiological aspect of SVB. However, it should be noted that this interpretation is subject of debate already for adults HRV and even more for the fetal developmental stage. Therefore, the consideration as long-term/short-term ratio might be more appropriate for both beat-to-beat related and CTG data. The principle of complementary risk scoring recently proposed based on the analysis of several fMCG study data sets (Hoyer *et al* 2019) can simply be transferred to CTG-based HRV indices as proposed here.

The following limitations of the present work should be taken into account. The simulation of the CTG-equivalent preprocessing of fMCG data uses exactly identified QRS complexes rather than sonographic reflection and, therefore, ignores the uncertainty of beat interval estimation from the autocorrelation function. Hence, the results presented here are likely to be too optimistic. Due to the retrospective design, dropouts due to bad signal quality of CTG and fECG recordings under routine conditions may have been underrepresented in this preselected data. Since the ANS is a complex system with branches that act both, antagonistically and synergistically, many HRV indices are highly correlated. Consequently, several multivariate models with similar precision can be found (Schmidt *et al* 2018b). Nevertheless, the present results show representative index sets.

By means of the overarching concept we tried to manage the following limitations on data availability: CTG and fMCG cannot synchronously be done. Even in the synchronous recordings of CTG and fECG the analyzable sections did not completely fit since the artifacts appeared at different times. The available data

sets came from different study centers. Nevertheless, the used overarching analysis considered all aspects in an adequate way with respect to the clinical use of HRV as diagnostic index of fetal autonomic tone.

A complete HRV profile would allow characterization of the behavioral state patterns and their HRV characteristics thoroughly. But the then required 24 h recordings are not practical. Active behavior is a criterion of fetal well-being. In practice, the lack of an active period during one hour of recording is considered as suspicious. Therefore, recordings up to one hour until appearance of an active state are CTG routine and the active period is quantified. According to the high proportion of active states, the use of 30 min recordings is a reasonable compromise to identify suspicious cases (Hoyer *et al* 2017). Fetal movements may result in considerable signal loss during CTG recording. In contrast, over-representation of vagal short-term characteristics during periods of quiet sleep may enhance the differences between fMCG and CTG characteristics. Previously we described clearly increased SVB in FGR fetuses during quiet sleep in fMCG recordings (Schneider *et al* 2006). In the present work during active sleep the SVB was increased in fMCG data only. Corresponding CTG based long-term/short-term ratio did not reach significance. Restricting the analysis to the more rarely occurring episodes of quiet sleep would result in remarkable dropout rates when the recording times are limited to 30–60 min. We did not analyze whether pathophysiologically important indices of vagal control during quiet sleep are lost in CTG with respect to FRG or any other developmental disturbances.

The autonomic components underlying short-term and SVB (long-term/short-term ratio) indices of CTG have to be described more precisely and understood in comparison to the established electrophysiological fHRV. Subsequent clinical studies of fetuses with other relevant developmental and health problems are necessary to confirm, refine and generalize the methodology proposed here. The present findings substantiate a fundamental extension of CTG-based fHRV analysis beyond the established long-term indices STV and LTV (FIGO 2011).

In summary, the results demonstrate the transferability of the established electrophysiological HRV methodology and indices to CTG recordings. It has the potential of reasonably enhancing clinical diagnosis of fetal autonomic tone. This methodology has to be validated in subsequent multicenter clinical studies on further patient entities. A further advantage could be that equivalent or related indices and study data sets, obtained from fMCG could be used in overarching data bases and improve sample size and quality of clinical CTG studies and vice versa.

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