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Correlation of short-term variation derived from novel ambulatory fetal electrocardiography monitor with computerized cardiotocography

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CONTRIBUTION

What are the novel findings of this work?

Short-term variation captured by a self-applied non-invasive fetal electrocardiography monitor is highly correlated with short-term variation obtained by computerized cardiotocography. Inaccuracies from signal loss can be reduced or corrected, and fetal heart rate monitoring regimes can be tailored to optimize signal quality and correlation.

What are the clinical implications of this work?

We identified key technological and algorithmic issues, and developed strategies to mitigate disparities between computerized cardiotocograph and non-invasive fetal electrocardiography. These together with evidence-based monitoring standards, are promising steps towards the development of safe and effective home fetal heart rate monitoring.

ABSTRACT

Objectives: The objective of this study is to compare short-term variation (STV) outputs from a novel self-applied non-invasive fetal electrography (NIFECG) with hospital computerized cardiotocography (cCTG) monitors. Technological and algorithmic limitations, as well as mitigation strategies will be evaluated.

Methods: This prospective cohort study took place in a tertiary London hospital. Women with a singleton pregnancy over 28+0 weeks' gestation attending hospital for cCTG assessment were monitored with both NIFECG and cCTG simultaneously for up to one hour. Post-processing of NIFECG using various methods of filtering produced NIFECG STV (eSTV) values, which were compared with cCTG STV (cSTV) outputs. Linear correlation, mean bias, precision, and limits of agreement (LoA) were assessed, using different methods of STV computation and mathematical correction.

Results: 306 concurrent NIFECG and cCTG traces were collected from 285 women. Fully filtered (F-filtered) eSTV was very strongly correlated with cSTV (R=0.911, p<0.001), but only generated results in 142/306 (46.4%) of one-hour traces due to the removal of those with lower-quality signals. Partial filtering generated more eSTV results (98.4%), but with a weak correlation to cSTV (R=0.337, p<0.001). STV difference (eSTV – cSTV) increased with signal loss, where in traces with ≥60% signal loss, the values became highly discrepant. Removal of traces with ≥60% signal loss resulted in a higher correlation with cSTV, whilst generating eSTV results for 65% of traces. Correcting these remaining eSTV values for signal loss using linear regression further improved correlation with cSTV (R=0.839, p<0.001).

Conclusions: The causes of STV discrepancy mandate the need for signal filtering, exclusion of poor-quality traces and eSTV correction. With such correction, the data demonstrate the device's ability to produce eSTV values highly correlated to the cCTG cSTV readings. This evidence-base for NIFECG monitoring and interpretation is a promising step forward in the development of safe and effective home FHR monitoring.

INTRODUCTION

Stillbirth is a devastating outcome of pregnancy, and efforts to reduce its rates are of intense public health interest[1]. Antenatal fetal surveillance to prevent demise is largely based on hospital confined methods such as ultrasound biometry, fetal Doppler assessments, and cardiotocography (CTG). Despite inter and intra-observer variation and the potential for clinical misinterpretation, CTG remains widely used in many hospitals across the globe[2]. Computerized CTG (cCTG) overcomes these challenges through an in-built processing algorithm generating numerical values for physiological fetal heart rate (FHR) parameters, thereby permitting standardized interpretation[3–7]. The use of cCTG has been shown to lead to a significant reduction in perinatal mortality compared to traditional CTG[2].

Interaction between the autonomic nervous systems is reflected in FHR variability, and a reduction in its bandwidth can be indicative of its suppression in chronic hypoxemia[8–10]. Short-term variation (STV) is numerical quantification of smoothed FHR variability, and the validation of cCTG STV in fetal hypoxemia detection has led to the development of widely-used standards in cCTG monitoring of high-risk women[8,9,11]. However, limitations in the number of cCTG platforms available, clinical expertise to apply the monitor and availability of appointments restrict the capacity to monitor high-risk pregnancies as frequently as required.

Non-invasive fetal electrocardiography (NIFECG) captures fetal and maternal PQRST complexes through the maternal abdomen. Not only does this have the potential to generate true beat-to-beat variability, but can also minimize fetal-maternal heart rate confusion, and is unaffected by fetal position or maternal habitus[12–16]. These theoretical benefits raise the possibility of its use out-of-hospital with self-application, thereby increasing surveillance without increasing service demands. However, due to technical challenges in small amplitude fetal R waves, and its susceptibility to interference and artefacts, this technology has been limited to research use[17,18]. In order to assess the potential for self-applied NIFECG to be used in the remote setting, it will need to be bench-marked against cCTG to identify areas for research and development.

The objective of this study is to compare STV outputs from a novel self-applicable NIFECG with the cCTG. Technological and algorithmic limitations, as well as mitigation strategies will be evaluated.

METHODS

This pilot prospective cohort study took place at St George's University Hospitals NHS Foundation Trust, London. Women with a singleton pregnancy over 28+0 gestation who presented to Day Assessment Unit requiring cCTG monitoring for any clinical indication were eligible. Women unable to consent or fitted with a pacemaker, with major fetal structural or genetic abnormalities, or those in labor were excluded. Recruitment took place from June 2021 to June 2022, and study procedures were followed according to study protocol[19].

Signal acquisition

Concurrent monitoring with both Huntleigh Sonicaid FM800 Encore Fetal monitor (Huntleigh Healthcare Ltd., Cardiff, UK) and NIFECG were performed for up to 60 minutes. NIFECG signals were captured using femom™ – a new self-applicable monitor developed by Biorithm Pte Ltd. consisting of a pod and a spreader, which allows easy attachment and removal of 5 gel electrodes for each monitoring session. This device is designed to be used in the remote setting, particularly by women requiring frequent monitoring, with a potential of self-application and production of automated FHR outputs. Through Bluetooth connection, raw ECG traces were displayed on 4 channels on a software installed on a mobile device. Data acquired were extracted in BioCapture recording files (bcrx), which were in turn exported as comma separated value (csv) files following signal processing, allowing numerical displays of FHR values per 0.25s epoch. Comparative csv files were also derived from each concurrent cCTG trace. Researchers and clinicians received no information from the NIFECG at the time of monitoring, and management plans were made from the cCTG outputs.

Signal processing

NIFECG post-processing took place after monitoring, and the trace was sampled at a frequency of 500Hz. Several steps including de-noising, maternal signal enhancement, maternal R peak detection, maternal signal removal, fetal signal enhancement, and fetal R peak detection were performed to generate FHR. FHR was in turn sampled at 4Hz and expressed as an FHR value within each 0.25 second epoch. cCTG uses autocorrelation, which does not detect individual heart beats but as a single representative periodicity value calculated on multiple beats. Therefore, smoothed FHR values were also produced at a frequency of 4Hz[9].

cCTG STV (cSTV) values were automatically produced by the Dawes-Redman algorithm for each trace. This algorithm consisted firstly of removing minutes containing all or part of a deceleration, or minutes with >50% signal loss. Pulse intervals (milliseconds (ms)) were averaged within 3.75 second epochs, and differences between each successive epoch were

then averaged over each minute. These averaged minute epochal differences were in turn averaged over the entire trace to produce the cSTV[4,9,20].

For NIFECG, 2 sets of STV (eSTV) data were produced – namely Fully-filtered (F-filtered) and Partially-filtered (P-filtered) eSTV, as outlined in Figure 1. Both sets of eSTV incorporates the Dawes Redman algorithm into its computation. The first step in both eSTV computations uses an outlier filter. Each trace time window was removed if the averaged pulse interval was outside expected range, similar to the initial step used by Dawes-Redman[4,9,20]. The F-filtered eSTV then proceeded to using a further series of filters, where firstly, epochs with >50% of pulse intervals >2000 or <250ms (FHR <30 or >240bpm) were discarded. Minutes with >50% discarded epochs were in turn removed, and traces with >50% removed minutes did not generate an eSTV result. This results in eSTV generation only in traces with the least signal loss.

Signal loss is defined as FHR outliers <30 or >240bpm, as FHR outside this range will mostly be due to missed R waves or artefact leading to falsely high FHR, and unlikely representative of true FHR. These values are therefore removed from eSTV analysis. FHR outliers in each 0.25s epoch is termed E240 signal loss (240 epochs per minute), and the presence of one outlier in a 3.75s epoch is termed E16 signal loss (16 epochs per minute). This aims to differentiate signal loss according to the default processing method (E240), and the signal loss processing method used by Dawes *et al.* (E16)[4]. Both are calculated as the proportion of discarded to accepted epochs in the entire trace expressed as a percentage.

Informative minutes are defined as the proportion of minutes with accepted signal within the total monitoring duration. This is calculated using the equation: total minutes – (total minutes x % signal loss/100). These are compared against the STV difference (eSTV – cSTV) between the two monitors.

Statistical analysis

Descriptive data were presented as median and interquartile ranges (IQR) for continuous variables, and number and percentages for categorical variables. Linear regression using STV difference between the devices as dependent variable, and signal loss as independent variable was performed. Predicted STV differences (Y) using the regression equations were generated, and corrected eSTV values were derived from the equation (eSTV – Y). Linearity of STV values from the two devices produced by various methods of computation were established using Pearson's correlation coefficient, after confirming normality using the Kolmogorov-Smirnov test. Accuracy and precision analysis were carried out to assess the mean bias, precision, and 95% upper and lower limits of agreement (LoA), for each method

of STV computation. Statistical software package SPSS v28.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. *P*-values < 0.05 were considered significant.

RESULTS

Concurrent NIFECG and cCTG monitoring were undertaken in 285 women, with 306 traces collected. This study population was also used to investigate NIFECG signal loss parameters as well as phase-rectified signal averaging (PRSA) indices, and the maternal and pregnancy characteristics are shown in Table 1. No safety issues were reported during the study period. Table 2 outlines the key outcome measures in the collected traces.

Median eSTV in F-filtered and P-filtered NIFECG were 9.2ms (IQR 7.6 – 11.4ms) and 10.7ms (IQR 8.6 – 13.7ms) respectively. Equivalent cCTG median cSTV was 9.9ms (IQR 7.9 – 12.3ms). eSTV outputs were generated in 142/306 (46.4%) traces using the F-filtered processing method, and 301/306 (98.4%) traces using the P-filtered processing method. cSTV values were generated for all cCTGs traces. Linear correlation between P-filtered eSTV and cSTV was weak (R=0.337, p<0.001) (Table 3). Mean bias, precision, and LoA were 1.57ms, 4.86ms, and -7.96 to 11.1ms respectively. Conversely, a very strong linear correlation was evident between the F-filtered eSTV and cSTV (R=0.911, p<0.001) (Figure 2). Minimal mean bias, high precision, and narrow LoA were also evident (-0.86ms, 1.18ms, -3.17 to 1.45ms respectively) (Figure 3).

Despite the high correlation, low outputs of eSTV using the F-filtered processing method (46.4%) prompted further analyses of the eSTV values produced using the P-filtered method. STV difference (eSTV – cSTV) for each trace was compared against both E240 and E16 signal loss for the same trace (Figures 4 and 5, respectively). An increase in STV difference is observed when E240 signal loss rises above 60%, and a similar increase is seen in E16 signal loss rises above 50%. 200/306 (65.4%) NIFECG traces had E240 signal loss ≤60%. Removing all traces with >60% E240 signal loss, linear correlation of these P-filtered eSTV values with cSTV was improved (R=0.785, p<0.001). A higher proportion (225/306 (73.5%)) of NIFECG traces had E16 signal loss ≤50%. Removing traces with >50% E16 signal loss also resulted in higher STV correlation than initially noted with the full dataset (R=0.683, p<0.001), but lower than STV correlation in traces with ≤60% E240 signal loss. Accuracy and precision analysis are displayed in Table 3.

Linear regression analysis using STV difference in the remaining traces as the dependent variable and signal loss as the independent variable were performed for both methods of signal loss computation. Predicted STV differences using regression equations in traces with ≤60% E240 signal loss and ≤50% E16 signal loss were generated (R^2 0.272, p<0.001, and R^2 0.280, p<0.001, respectively). Corrected eSTV values were in turn formulated by subtracting the predicted differences from the original eSTV. Linear correlation between corrected eSTV in traces with ≤60% E240 signal loss against cSTV was stronger than pre-correction (R=0.839,

p<0.001). Similar findings were seen in the correlation between corrected eSTV in traces with ≤50% E16 signal loss against cSTV (*R*=0.748, p<0.001). Mean bias, precision, and LoA were also improved following correction (Table 3).

The relationship between informative minutes and STV difference is demonstrated in Figure 6. This shows that increasing duration of monitoring, and hence increasing informative minutes, can reduce STV difference.

DISCUSSION

Summary of study findings

STV correlation between NIFECG and cCTG is significantly influenced by methods of signal processing. Fully filtering NIFECG traces results in excellent correlation, but a lower yield of eSTV outputs due to rejection of a significant number of traces. Conversely, removal of filters leads to high eSTV yield from NIFECG but weak correlation with cSTV, as eSTV becomes increasingly discrepant from cSTV with increasing signal loss. Following removal of poor-quality traces, correction for signal loss in the remaining traces further improved the correlation, whilst also increasing eSTV yield from full filtration.

Comparison with existing literature

Seliger *et al*. compared STV correlation between Huntleigh cCTG and Monica AN24 NIFECG monitors in 26 pregnancies from 24 weeks[12]. A threshold of <50% signal loss was used to exclude traces they deemed unsuitable for analysis. 20/26 (77%) traces met criteria for analysis, and in these traces, a similar filter removing two-minute windows containing >50% signal loss was also implemented. This led to a comparable agreement to our findings when filters were applied[12]. The authors concluded that FHR variability requires high quality beat-to-beat signals to generate reliable data[12].

Another study compared STV using different computations in 67 term pregnancies, using MONAKO (CTG) and KOMPOREL (NIFECG) systems. Signal loss was defined as FHR=0bpm in 0.25s epochs, and traces with >30% signal loss were excluded. A filter was also applied where segments with >80% signal loss were excluded. Multiple recordings were taken for each woman, and only the best used for analysis. Given these different methods, a very low signal loss of 1.8% was reported for NIFECG, after excluding 7 women with uninterpretable traces. Despite filtering, post-processed eSTV values were significantly higher than cSTV, with a mean percentage difference of 56%[21]. This is likely due to their signal loss definition, where spuriously high FHR values due to artefacts were regarded as true FHR. Nonetheless, the authors concluded that NIFECG likely represent true STV, whilst STV from CTG were incorrectly underestimated[21].

Limitations of signal processing

Although NIFECG has the potential advantage of producing superior temporal resolution with a high sampling frequency, it is also prone to artefacts and interference, giving rise to false fetal R waves and thus fluctuations in FHR[12]. Low fetal signal-to-noise ratios resulting from poor conductivity through several fetal and maternal abdominal layers, and artefacts from movements, conduction pathways and electrical surroundings all play a role in limiting signal

accuracy[17,18]. cCTG on the other hand, does not have the ability to sample at high frequencies, and therefore relies on autocorrelation to provide a more consistent rate[9,12]. The difference in technology will undoubtedly lead to a discrepancy in the STV values generated.

In our dataset, high signal loss resulted in high eSTV values in our P-filtered traces, and hence greater STV difference between the two monitors. This demonstrates that signal loss, defined as FHR outliers, creates discrepancy between epochs, and thereby falsely increasing the eSTV. Defining FHR outliers as <30 or >240bpm, in keeping with that used by commercial monitors, rates outside this range were considered not to be true FHR[22,23]. To the best of our knowledge, the classification of outliers or its elimination process within the cCTG internal algorithm is not known. Although such outliers were not included in the epochal averaging of FHR, many FHR samples lay on the borders of the valid FHR range. The outlier filter removed trace time windows where averaged FHR were found to be out of expected range. Despite this step, many 30s windows also lay on the borders of this range. Furthermore, by excluding outliers, traces with high signal loss are left with very little remaining data to calculate eSTV, leading to additional discrepancies to cSTV.

Mitigating technical limitations and future research

Given the nature of NIFECG technology, eSTV should only be used in high quality traces (≤60% E240 signal loss), with a filtering method to eliminate outliers. As signal loss plays a major role in eSTV accuracy, eSTV mathematical correction for signal loss should also be considered. Although this raises the issue of no eSTV result in poor quality traces, a method to overcome this can be to prolong monitoring time. As NIFECG delivers no energy, this can be performed safely. As the aim of FHR monitoring is to establish the presence of an active fetal state, the presence of the latter within any period of time should be acceptable. The Dawes-Redman criteria uses a minimum of 10 minutes demonstrating normal FHR variability to determine wellbeing[4,20]. A similar strategy can be used, where normal eSTV obtained within any 10 minutes of high signal quality may be accepted as confirmation of fetal wellbeing regardless of the overall signal loss in the trace. Conversely, if more than 50 minutes of high quality signal demonstrate low eSTV, it should be deemed as a cause for concern[4,20].

Detailed analysis of signal quality, including the impact of fetal-maternal factors have been described in a separate paper. Lower gestation age had a significant impact on signal loss (beta = -2.91, 95% CI: -3.69 to -2.12, p<0.001), and a reduction in interference was observed on changing the polymer spreader which attaches the electrodes (24% vs 9%, p<0.001). Preliminary pilot data also suggests that signal acquisition outside the hospital environment results in less electrical noise/interference. Furthermore, in clinical use, multiple applications of the device at home may allow improved signal acquisition. However, further research into

signal quality in the home environment, together with device optimisation will shed light on the device potential.

Another method of fetal autonomic assessment described is PRSA. This assesses quasi-periodic oscillations in non-stationary, noisy signals, and therefore, accounting for and eliminating artefacts as part of its signal processing algorithm[24–26]. This method has been used in both cCTG and NIFECG, and have shown possible superiority over STV in detecting evolving hypoxia[27]. PRSA therefore may be more promising in its use in remote NIFECG, with less reliance on high signal acquisition. Research comparing PRSA outputs from a self-applicable NIFECG with outputs derived from cCTG, should be performed to enable use in clinical practice.

Conclusions

The systematic evaluation of eSTV acquisition using a self-applicable ambulatory NIFECG monitor has not only highlighted the potential of the device, but pin-pointed the technical challenges that have to be overcome to permit clinical use. The causes of STV discrepancy mandate the need for signal filtering, poor quality trace exclusion and STV correction. With such correction, the data demonstrate the device's ability to produce eSTV values highly correlated to the cSTV, and provide a rationale for thresholds used for trace exclusion. This study sets the evidence-base for NIFECG monitoring and interpretation for the development of safe and effective home FHR monitoring strategies.

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FIGURE LEGENDS

Figure 1: Outline of NIFECG short-term variation (eSTV) computation. Fully filtered (F-filtered) eSTV values are produced from all steps generated by the entire flow chart, whilst partially filtered (P-filtered) values do not include the dashed boxes.

Figure 2: Scattergram displaying correlation of F-filtered NIFECG STV compared with cCTG STV.

Figure 3: Bland-Altman plot displaying STV difference against STV mean generated by F-filtered NIFECG and cCTG.

Figure 4: Scattergram demonstrating the correlation between STV difference (P-filtered NIFECG – cCTG) and E240 signal loss.

Figure 5: Scattergram demonstrating the correlation between STV difference (P-filtered NIFECG – cCTG) and E16 signal loss.

Figure 6: Scattergram demonstrating the correlation between STV difference (P-filtered NIFECG – cCTG) and viable minutes.

Table 1: Table demonstrating maternal and fetal characteristics of the study population.

Demographics	Study population (n=285)
Age (years)	32.0 (30.0 – 36.0)
Height (cm)	163.9 (160.0 – 169.0)
Weight (kg)	68.4 (60.2 – 81.6)
BMI	25.3 (22.6 – 29.5)
Ethnicity	
White	182 (63.9%)
Black	34 (11.9%)
Asian	51 (17.9%)
Mixed/other	18 (6.3%)
Gestational age (weeks + days)	37^{+1} (34^{+5} – 39^{+3})
Estimated fetal weight centile	46.0 (25.0 – 67.0)
Small for gestational age pregnancy	27 (9.5%)
Hypertensive disorders of pregnancy	35 (12.3%)
Diabetic pregnancy	41 (14.4%)

Data are given as median (interquartile range) or number (%). BMI, body mass index.

Table 2: Table demonstrating key outcome measures of all traces collected.

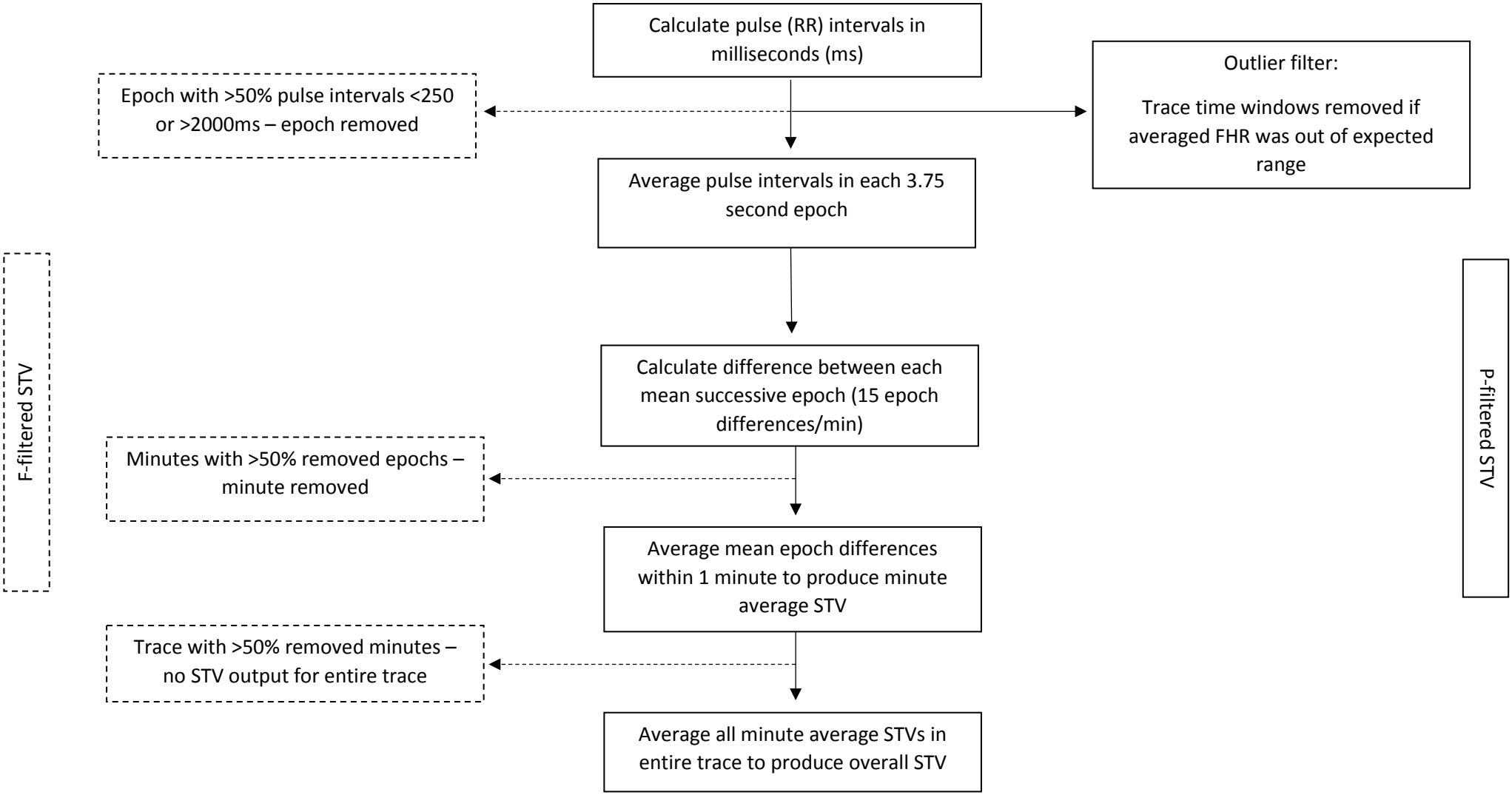
Outcome measure	Trace results (n=306)
Monitoring duration (min)	60.0 (42.0 – 60.0)
	STV (ms)
cCTG (n = 306)	9.9 (7.9 – 12.3)
NIFECG P-filtered (n = 301)	10.7 (8.6 – 13.7)
NIFECG F-filtered (n = 142)	9.2 (7.6 – 11.4)
	NIFECG signal loss (%)
E240	34.0 (7.5 – 72.1)
E16	18.5 (2.1 – 52.9)

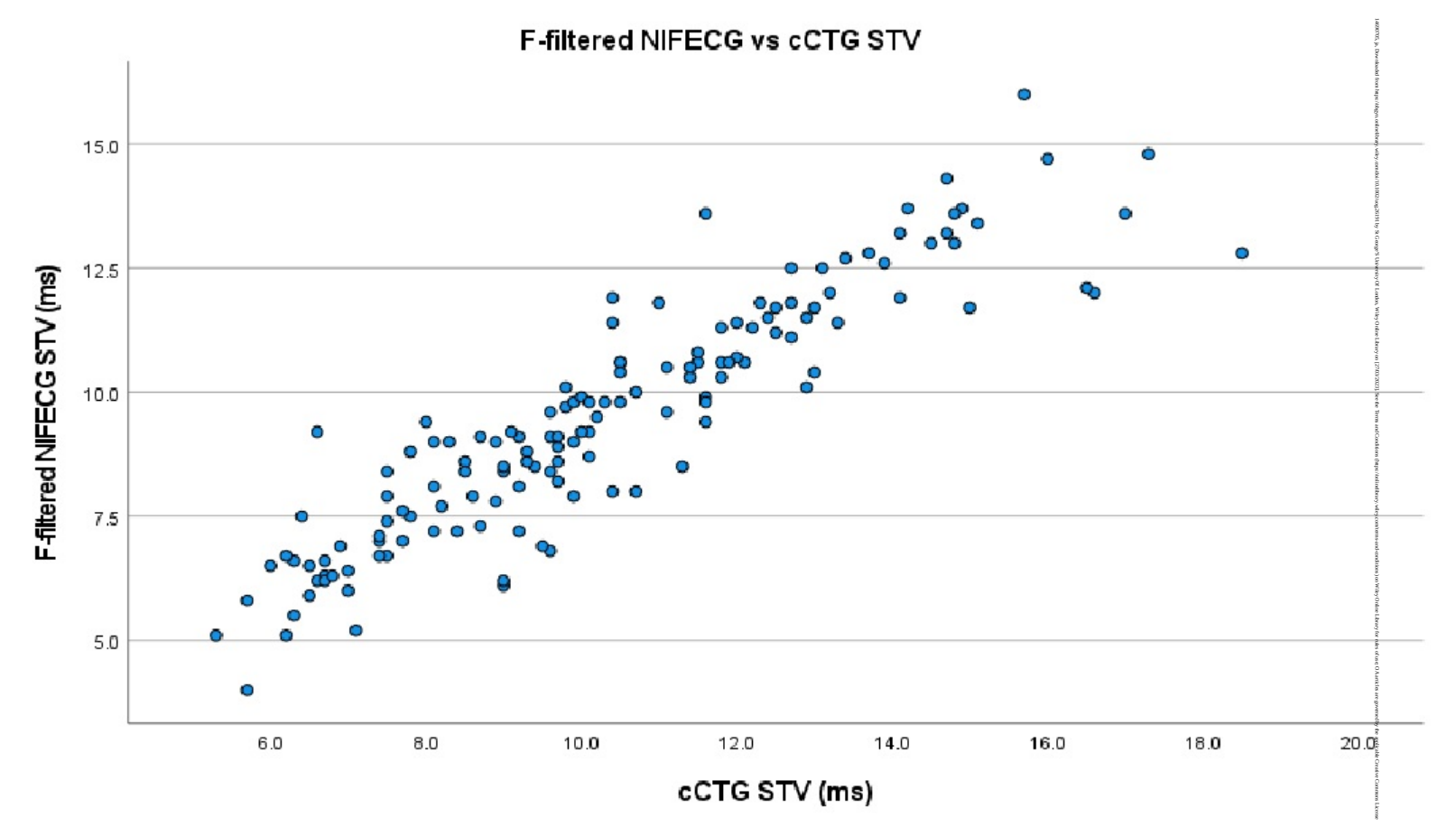
Data are given as median (interquartile range) or number (%). P-filtered are traces generated through partial filtering, and F-filtered are traces generated through full filtering. E240 signal loss are defined as FHR outliers (<30 or >240bpm) within a 0.25 second epoch, E16 signal loss are 3.75 second epochs which contain all FHR outliers.

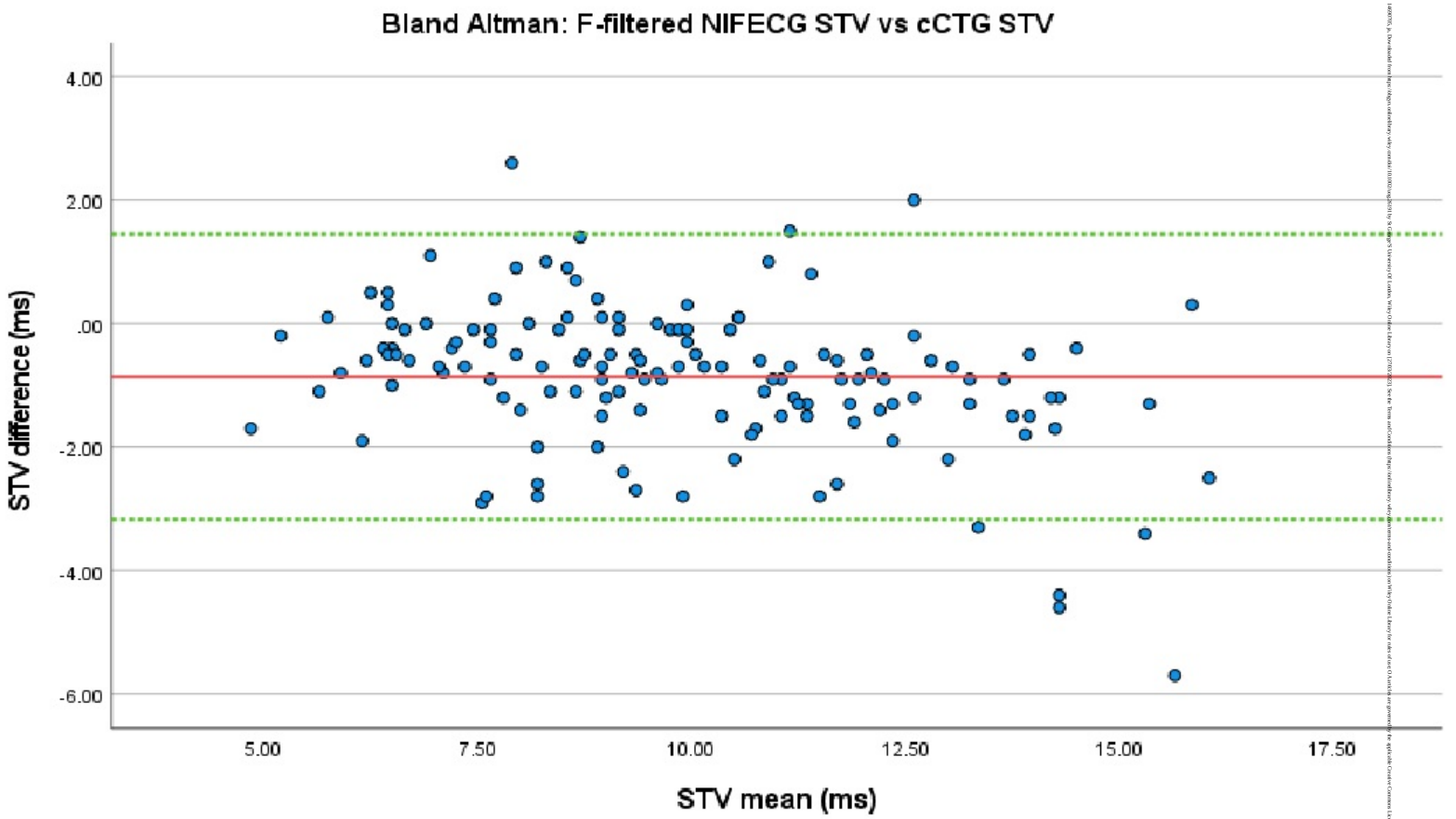
Table 3: Table showing linear correlation of NIFECG short-term variation (eSTV) with cCTG short-term variation (cSTV).

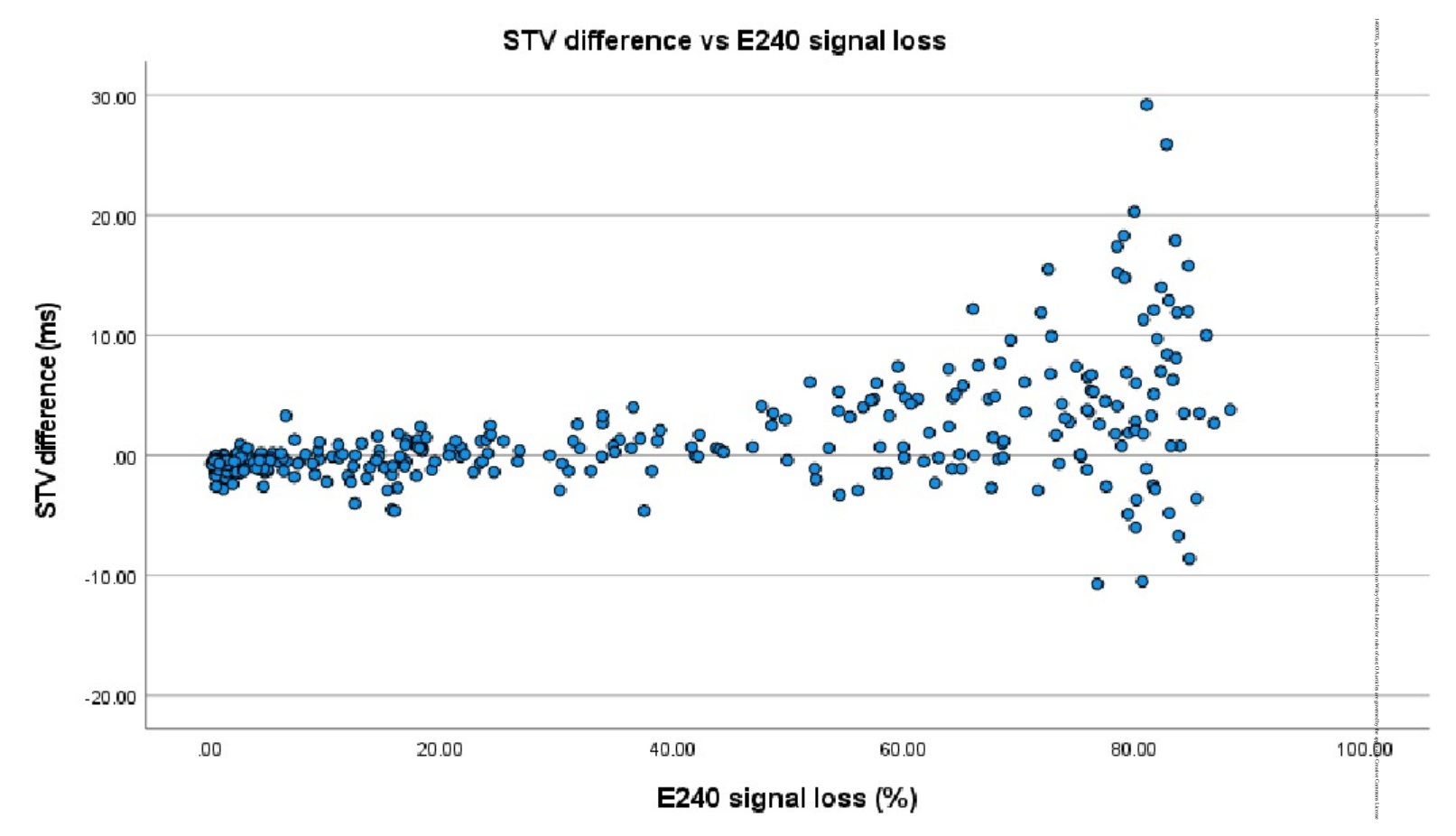
	P-filtered STV	P-filtered STV with ≤60% E240 signal loss	P-filtered STV with ≤60% E240 signal loss corrected	P-filtered STV with ≤50% E16 signal loss	P-filtered STV with ≤50% E16 signal loss corrected	F-filtered STV
Traces with STV acquired (%)	301 (98.4%)	200 (65.4%)	200 (65.4%)	225 (73.5%)	225 (73.5%)	142 (46.4%)
Pearson's R coefficient	0.337	0.785	0.839	0.683	0.748	0.911
p value	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Mean bias (ms)	1.57	0.05	0.00	0.39	0.00	-0.86
Precision (ms)	4.86	1.93	1.642	2.42	2.04	1.18
Upper LoA (ms)	11.1	3.82	3.22	5.12	4.01	1.45
Lower LoA (ms)	-7.96	-3.72	-3.22	-4.34	-4.01	-3.17

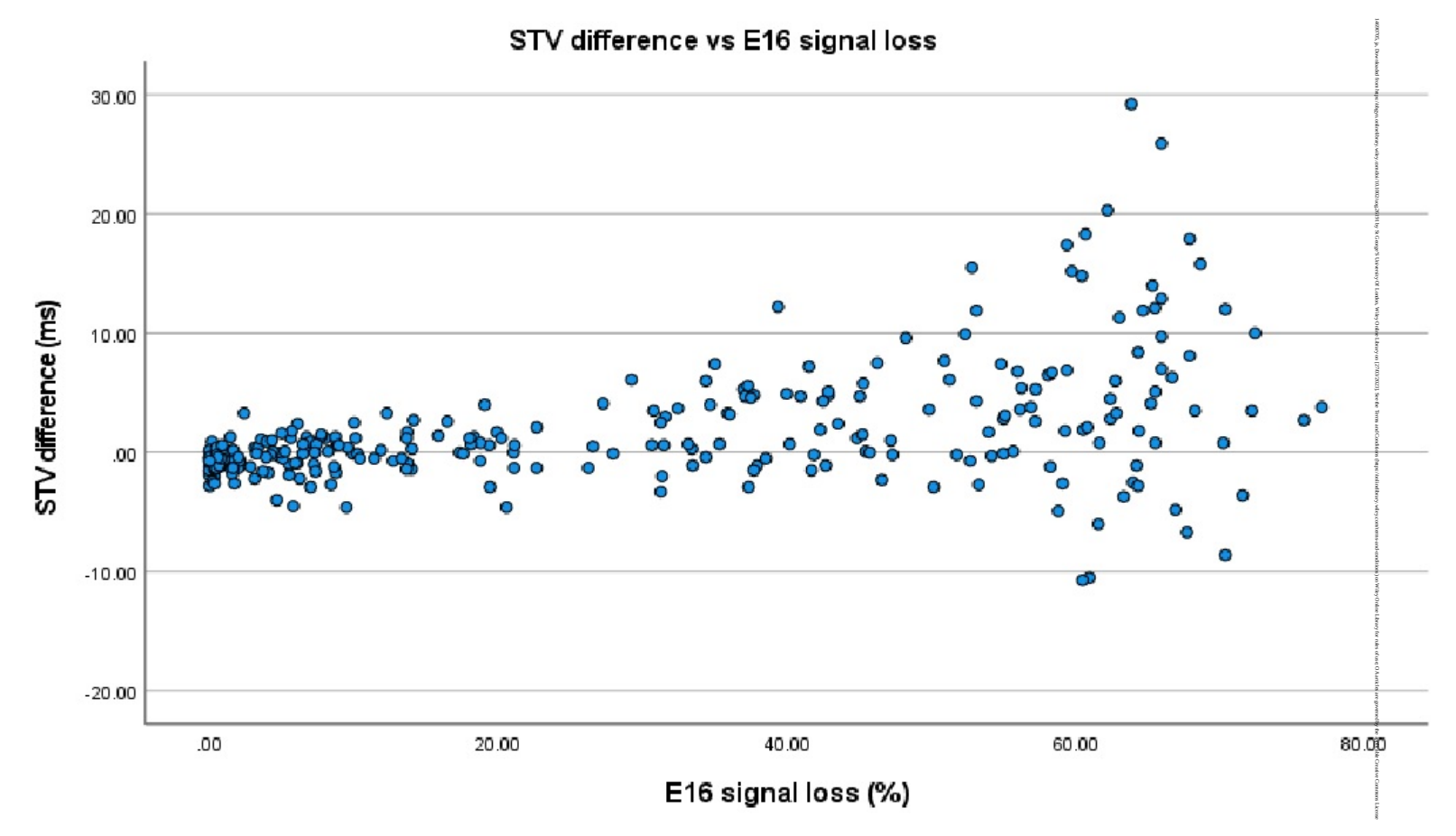
P-filtered are traces generated through partial filtering, and F-filtered are traces generated through full filtering. E240 signal loss are defined as FHR outliers (<30 or >240bpm) within a 0.25 second epoch, E16 signal loss are 3.75 second epochs which contain all FHR outliers. Corrected eSTV are corrected for signal loss using linear regression equations. Mean bias, precision, upper and lower limits of agreement (LoA) for various methods of eSTV computation in comparison with cSTV are also displayed.

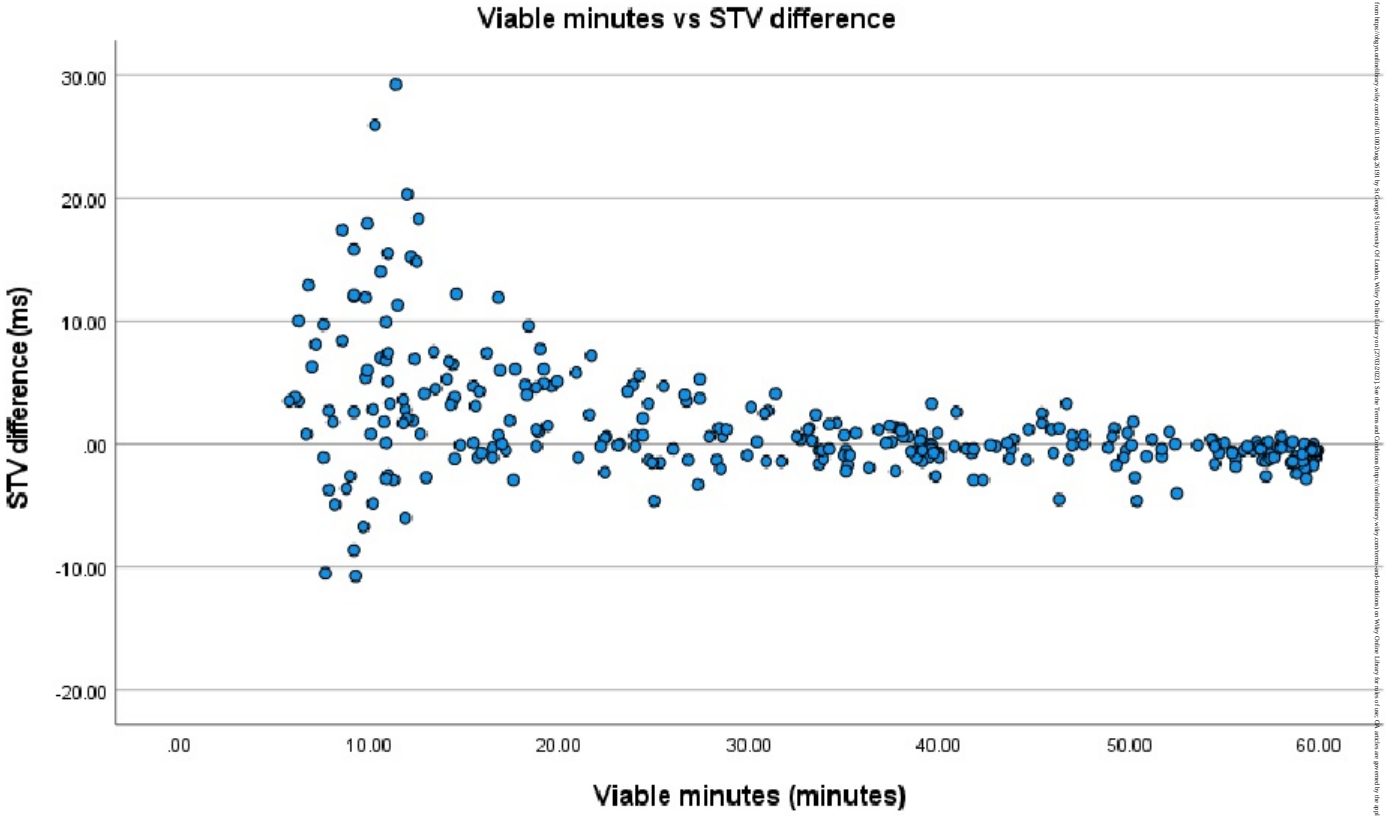



F-filtered NIFECG vs cCTG STV
F-filtered NIFECG STV (ms)
15.0
12.5
10.0
7.5
5.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
cCTG STV (ms)


Bland Altman: F-filtered NIFECG STV vs cCTG STV
4.00
2.00
.00
-2.00
-4.00
-6.00
STV difference (ms)
5.00
7.50
10.00
12.50
15.00
17.50
STV mean (ms)


STV difference vs E240 signal loss
STV difference (ms)
30.00
20.00
10.00
.00
-10.00
-20.00
.00
20.00
40.00
60.00
80.00
100.00
E240 signal loss (%)


STV difference vs E16 signal loss
STV difference (ms)
30.00
20.00
10.00
.00
-10.00
-20.00
.00
20.00
40.00
60.00
80.00
E16 signal loss (%)


Viable minutes vs STV difference
30.00
20.00
10.00
.00
-10.00
-20.00
STV difference (ms)
.00
10.00
20.00
30.00
40.00
50.00
60.00
Viable minutes (minutes)