Exploring the Relationship Between Intracavitary Electrohysterogram Characteristics from Contraction and Window Analysis

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Abstract: Assisted reproductive technologies are increasingly common due to the rising maternal age. One potential cause of embryo implantation failure is altered uterine peristalsis patterns. Intracavitary electrohysterography (IC-EHG) is a recent technique developed to characterize the electrophysiology of uterine peristalsis throughout the menstrual cycle. Two primary methodologies are employed for analysis: Contraction Analysis and Window Analysis. This study aims to examine the relationship between parameters describing the same characteristics of the signals using contraction and window analysis of 2, 4 and 10 minutes. Peristalsis was recorded at three different menstrual cycle phases from 10 fertile healthy women. Continuous 10 minutes recordings free of artifacts were selected. A very strong linear relationship ($R^2 \geq 0.95$) was found between the amplitude parameter from contraction (Root Mean Square (RMS)) and window (80th percentile of signal RMS envelope) analysis. For the spectral parameter (Median Frequency), the relationship was strong ($0.59 \leq R^2 \leq 0.75$), while for the non-linear parameter (Sample Entropy), it was moderate ($0.19 \leq R^2 \leq 0.29$). Strongest relationships were obtained with 2-minutes windows. The findings suggest that window analysis can accurately assess contraction intensity and, more moderately its spectral content; but basal segments in window analysis significantly influence the signal complexity parameter.

1 INTRODUCTION

The increasing maternal age in recent decades has led to a raise in infertility rates, often needing assisted reproductive technologies (Balasch, 2010). Congenital and acquired uterine anomalies, such as septate uterus or leiomyomas, are the most contributing factor in approximately 30 % of infertility cases (Brugo-Olmedo et al., 2001). Endometriosis and adenomyosis are closely related with infertility, since the appearance of endometrial tissue in atypical places alter the normal anatomy of the uterine tract. These uterine pathologies express a disturbed peristaltic pattern, since there exists a significant increase in the number and power of contractions (Leyendecker et al., 2022), which can further complicate reproductive outcomes by interfering with both sperm ascent and embryo implantation.

Therefore, studying and characterizing uterine peristalsis is crucial for developing effective therapies for reproductive disorders associated with abnormal uterine dynamics. Various techniques can be employed to monitor uterine contractions throughout

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the menstrual cycle. Intrauterine pressure (IUP) measurements are useful for obtaining mechanical parameters such as contraction frequency of occurrence, duration and amplitude (Benalcazar-Parra et al., 2019). However, this method does not provide information about spectral and nonlinear domain parameters, as well as may not be sensitive enough to capture low-intensity contractions that occur during the menstrual cycle. Imaging-based techniques such as transvaginal ultrasound (TVUS) or magnetic resonance imaging (MRI), can visualize waves propagating throughout the endometrium by watching video files at accelerated speed. In addition to requiring expert operator and the subjectiveness of the evaluation, the limitation of these techniques is that they can only characterize the frequency of occurrence and directionality of contractions, without obtaining intrinsic contraction parameters (van Gestel et al., 2007), (Togashi, 2007). All of these techniques have been used to monitor uterine contractions during menstrual cycle, as well as during pregnancy and childbirth. Nevertheless, another technique known as electrohisterography (EHG), allows the measurement of myometrial electrical activity from the abdominal surface during pregnancy (Diaz-Martinez et al., 2024) and childbirth (Alberola-Rubio et al., 2017). Intracavitary electrohysterography (IC-EHG) emerged due to the need to study the electrophysiology of low intensity uterine peristalsis during the menstrual cycle (Alberola Rubio, 2021). This technique enables the exploration of all parameters assessed by the previous techniques, in addition to those in the spectral and nonlinear domains.

When characterizing myometrial electrical activity using EHG, two primary approaches can be followed: window analysis (WND) or contraction analysis (CTR) (Díaz-Martinez et al., 2021), (Mas-Cabo et al., 2019). In the former, fixed-length segments are selected to encompass continously physiological information from the signal. It is crucial to ensure that these segments are free from artifacts or interference that could distort parameter calculations. Conversely, in contraction analysis, parameters are computed over the signal bursts, requiring prior identification of these contractions, often a manual, subjective and time-consuming task (Mas-Cabo et al., 2019).

The aim of this study is to investigate the degree of association between parameters characterizing the same characteristics of IC-EHG signals when using either CTR or WND analysis.

2 MATERIALS AND METHODS

2.1 Database Composition

This study included 30 IC-EHG signals acquired from 10 volunteer women at the Ovodonation Unit of the Valencian Infertility Institute from Valencia, Madrid and Barcelona. Participants of reproductive age (18-34 years) were recruited if they exhibited regular menstrual cycles, a body mass index between 18.5 and 25 kg/m², and a documented history of fertility. Exclusion criteria included uterine malformations, pregnancy, sexual intercourse within the previous 48 hours, use of any contraceptive method, severe dysmenorrhea, irritable bowel syndrome, or a history of ectopic pregnancies.

Following enrollment, each participant underwent three recordings: one during the mid-follicular phase (MF, 6-8 days post-menses), another during the early luteal phase (EL, 2-4 days post-LH surge), and a final one during the late-luteal phase (LL, 7-9 days post-LH surge). All participants were provided with detailed information about the study and gave their informed consent. The study adhered to the guidelines outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the *Hospital Universitari i Politècnic La Fe* (Valencia, Spain) under registration number 2023-108-1.

2.2 Signal Recording and Preprocessing

All recordings were conducted using a disposable 6-pole multipolar catheter for the detection of non-pregnant myometrial electrical activity (Alberola Rubio, 2021). The tip electrode was in contact with the uterine fundus, while the distal electrode was closer to the cervix. The later served as the reference electrode as smooth muscle cells content decreases towards the cervix (Wray & Prendergast, n.d.). Monopolar signals from each electrode were amplified with a bandwidth of 0.1 to 30 Hz and acquired for 30 minutes at a sampling rate of 500 Hz.

For this study, a bipolar signal from the uterine fundus region was obtained as the difference between the signals capturated by the first two catheter electrodes. The signal was digitally filtered in the fast wave bandwidth (Devedeux et al., 1993), (Fele-Žorž et al., 2008). For each recording, a segment of 10 minutes of continous physiological information was carefully selected by consensus between two experts, avoiding artefacted signal segments

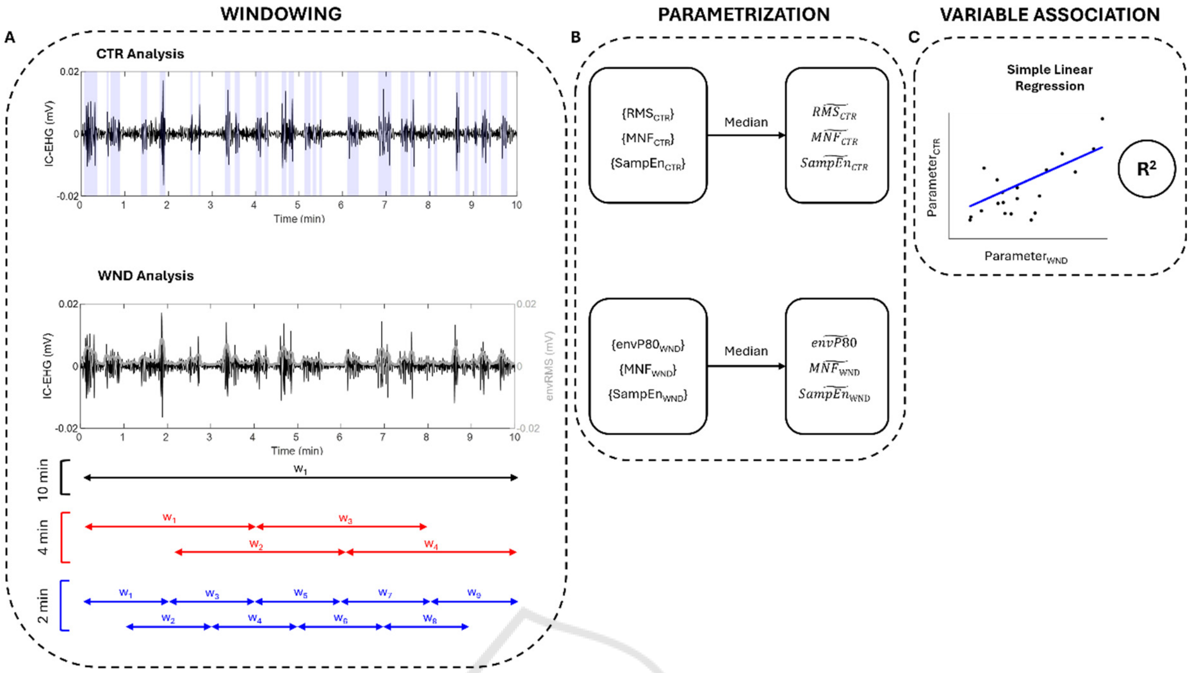

Figure 1: Signal analysis methodology. **A)** Windowing step with CTR and WND analysis. Contractions have been identified in CTR, whereas three different window sizes (10, 4 and 2 minutes) have been used in WND analysis. **B)** Amplitude, spectrum and complexity parameter calculation for each analysis. **C)** Simple linear regression for assessing the relationship between the same IC-EHG characteristics with CTR and WND analysis.

2.3 Windowing and Parametrization

Figure 1 illustrates the methodology employed in this study. Initially, a windowing step is implemented to identify the segments for analysis based on CTR o WND approaches. Subsequently, parameters are extracted from these segments and summarized at a recording level by their median value. Finally, a simple linear regression is performed for parameters that characterize same IC-EHG features with CTR and WND analysis.

As represented in Figure 1A, CTR analysis requires the identification of the start and end points of peristaltic waves. This was carried out by two experts in electrohysterographic recording and analysis. For each identified contraction, three widely used parameters were calculated to describe different aspects of the signal: signal amplitude/intensity, spectrum and complexity.

- **Root Mean Square (RMS_{CTR}):** is a robust measure for characterizing the intensity of the uterine myoelectrical activity. It is defined as the square root of the arithmetic mean of the squares of the values (Mohammadi Far et al., 2022).
- **Mean Frequency (MNF_{CTR}):** is a spectral parameter related with cell excitability (Mas-Cabo et al., 2020). It is computed as the sum of product of the IC-EHG power spectrum and the frequency divided by the total sum of the power spectrum (Phinyomark et al., 2012).
- **Sample Entropy ($SampEn_{CTR}$):** is a non-linear parameter which estimates signal complexity. It is computed as the negative natural logarithm of the probability that two sequences similar for *m* points remain similar at the next point, with a certain tolerance *r* and ignoring self-matches. Hyperparameters m=2 and r=0.1 have been chosen as suggested in (Radomski, 2010).

On the other hand, the WND analysis does not require precise identification of peristaltic events but does necessitate the setting of a hyperparameter, the window size. In this study, three window sizes were tested: 10, 4, and 2 minutes, with a 50% overlap (except for 10 minutes windows), represented by arrows of different color in Figure 1A. The following parameters were computed for each window of analysis.

To describe the intensity of the uterine myoelectric activity, it is common to create an envelope signal to analyze and characterize amplitude evolution of EHG signals (Chowdhury et al., 2024).

It was calculated using a 5-second moving RMS, computed sample by sample. Following the generation of this smoothed version, the 80th percentile of the envelope weas selected for each window ($envP80_{WND}$). This selection was based on a percentile sweep conducted with a step size of 5%, identifying the percentile that exhibited the strongest linear relationship with RMS_{CTR}. MNF_{WND} and $SampEn_{WND}$ were computed as in the contraction analysis, but on whole windows of the signal rather than on single contractions.

To summarize the information at the recording level, the median values of the contractions or window's parameters were calculated for each analysis as represented in Figure 1B.

2.4 Variable Association

A simple linear regression model was used to assess the relationship between the parameters derived from CTR and WND analysis that characterized the signal intensity, spectrum and complexity. The coefficient of determination (R^2) was computed to quantify the proportion of variance in the dependent variable that could be attributed to the predictor variable. This metric provides an indication of the strength of the linear association between the two variables, and it is the evaluation metric selected as shown in Figure 1C.

3 RESULTS

Figure 2 shows the scatterplots and linear interpolation curves between contractions parameters and their counterparts with window analysis using different window sizes. Complementarily, Table 1 shows the coefficient of determination (R^2) that quantifies the strength of the linear relationship between variables. Regarding amplitude parameters, a very strong linear association (R^2>0.95) was obtained between RMS_{CTR} and $envP80_{WND}$ for any window size as observed in Table 1. Moreover, as it can be appreciated in Figure 2A, the fitted lines for the three window sizes show intercepts close to zero and slopes slightly smaller than 1. Frequency domain parameters MNF_{CTR} and MNF_{WND} also showed a strong linear relationship between them. The maximum R^2 is obtained when using a window size of 2 minutes (R^2=0.75), followed by the 4-min window size (R^2=0.69). The strength of the relationship is s significantly reduced with a 10-min window size (R^2=0.59). Finally, complexity parameters $SampEn_{CTR}$ and $SampEn_{WND}$ show a weak relationship when using 10-min windows (R^2=0.19), and moderate for 2-min and 4-min windows (R^2=0.22 and 0.29, respectively). This can also be seen in Figure 2C, where it can be observed that the different measurements are quite scattered without being concentrated near the fit lines.

Table 1: Coefficients of determination (R^2) of associations between contraction and window analysis parameters using different window sizes.

	10 min	4 min	2 min
RMS_{CTR} vs $envP80_{WND}$	0.96	0.97	0.97
MNF_{CTR} vs MNF_{WND}	0.59	0.69	0.75
$SampEn_{CTR}$ vs $SampEn_{WND}$	0.19	0.29	0.22

Moreover, to assess the effect of menstrual phase in the analysis, same procedure has been carried out but splitting the population into 3 different subpopulations (MF, EL and LL), so that 10 recordings are analysed for each group. Table 2 shows the strength of association between same CTR and WND parameters depending on each menstrual phase.

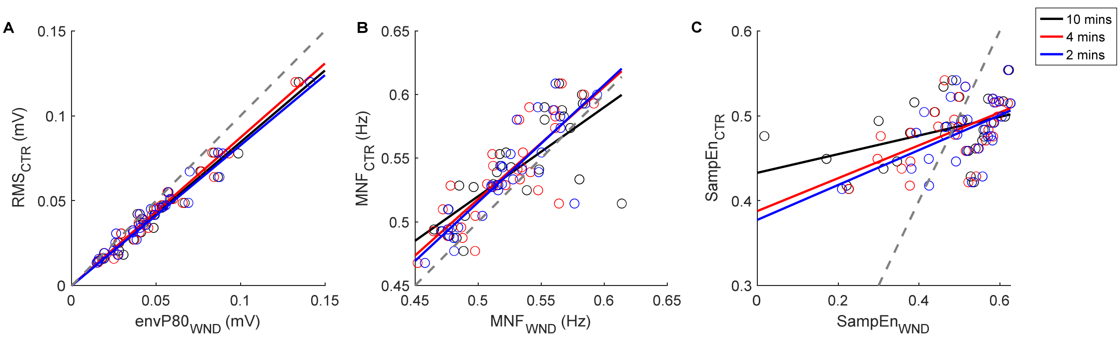

Figure 2: Scatterplot showing simple linear regression for the association between CTR and WND parameters when computed using different window sizes. Dashed line represents 1:1 relationship (identity).

Table 2: Coefficients of determination (R^2) of associations between CTR and WND parameters in subpopulations based on menstrual phase (MF: mid follicular, EL: early luteal, LL: late luteal).

		10 min	4 min	2min
RMS_{CTR} vs $envP80_{WND}$	MF	0.95	0.95	0.94
	EL	0.95	0.97	0.99
	LL	0.92	0.93	0.95
MNF_{CTR} vs MNF_{WND}	MF	0.92	0.91	0.92
	EL	0.21	0.49	0.56
	LL	0.77	0.54	0.81
$SampEn_{CTR}$ vs $SampEn_{WND}$	MF	0.55	0.56	0.55
	EL	0.23	0.51	0.46
	LL	0.08	0.12	0.12

It can be appreciated from Table 2 that amplitude parameters are highly correlated irrespective of the menstrual phase. However, some differences can be appreciated in frequency and non-linear parameters with respect to the menstrual phase. MNF_{WND} in early luteal phase do not correlate with MNF_{CTR} as in MF or LL. Similarly, $SampEn_{WND}$ and $SampEn_{CTR}$ do not show linear correlation when assessed in LL.

4 DISCUSION

As shown in Table 1, there is a strong correlation between amplitude parameters from contraction and window analysis. The window size for the WND analysis does not affect the strength of this association. Nevertheless, we believe it is preferable to use small window values, as spurious artifacts might appear and, by selecting the median $envP80_{WND}$ value across all windows, the analysis could be more robust to outliers caused by high-energy artifacts (Batista et al., 2016). According to Table 2, the menstrual phase does not influence the correlation between these two variables. While the intensity of uterine contractions varies throughout the menstrual cycle (Bulletti et al., 2004) under the influence of sexual hormones, the association between the two variables is robust to the influence of the cycle phase. Therefore, the coefficients of the simple linear regression could be used to predict the RMS_{CTR} parameter without the need for prior segmentation of peristaltic contractions.

Regarding the spectral parameters MNF_{CTR} and MNF_{WND}, there is a significant relationship between them. Generally, MNF_{CTR} values are higher than MNF_{WND} values (they lie above the identity line, Figure 2B). This should mainly be associated to the inclusion of basal segments in the calculation of MNF_{WND}. Basal segments are of lower power and hence the power of the whole signal is reduced in comparison to that of only contractions. Consequently, the more concentrated power in the lower frequencies of contraction segments is emphasized with respect of this reduced total power, yielding lower mean frequencies. Another aspect that can provoke differences between MNF_{CTR} and MNF_{WND} could be the difference in the frequency resolution. As can be seen in Figure 1, the duration of contractions is smaller than any window size (2, 4 or 10 mins), which modifies the frequency resolution for CTR and WND analysis. The smallest window size has the most similar frequency resolution to that of contractions and could also be contributing to obtaining the strongest relationship between spectral parameters derived from CTR and WND analysis. It is worth noting the low relationship between the two parameters in EL phase in comparison to that of MF phase. This could be related to differences in the electrophysiological conditions of uterine muscle in these two phases. More specifically, IUP recordings during EL phase have shown a greater rate of contractions and an elevated basal tone (Van Gestel et al., 2003), which may be attributed to altered cellular excitability in this phase, influencing the basal state. Further studies would be necessary for a more refined interpretation of these results.

Finally, a significant but moderate relationship exists between $SampEn_{CTR}$ and $SampEn_{WND}$. As illustrated in Figure 2, it is preferable to use shorter windows, of 2 or 4 minutes, as the regularity of the signal may vary throughout the recording or differ significantly between phases of the menstrual cycle, making it challenging to generalize the relationship between these variables across the entire menstrual cycle. Physiologically, a decrease in entropy can be interpreted as a result of increased coordination among myometrial cells (Mischi et al., 2018). Similar to findings regarding MNF, significant differences have been observed between SampEn of contractile and non-contractile segments in EHG recordings from pregnant women (Hao et al., 2019). While the behavior in non-pregnant uteri is not fully understood, it is likely that coordination among cells changes throughout the menstrual cycle for both contractile and non-contractile segments. Table 2 supports this hypothesis, as the correlation between $SampEn_{CTR}$ and $SampEn_{WND}$ decreases as the cycle progresses, being much lower in the luteal phase than the mid-follicular phase. This may be attributed to changes in the expression of gap junctions throughout the menstrual cycle. Estrogen, the dominant hormone during the follicular phase, promotes the formation of connexin 43 (the protein that makes up gap junctions, which facilitate the electrical communication between adjacent cells). In contrast, progesterone, which dominates the luteal phase, reduces the expression of connexin 43, leading to decreased cellular coordination during this phase (Condon et al., 2020).

This study has several limitations. The identification of the artefactual signal segments to be excluded from the analysis is carried out manually by two experts. In future studies, automatic classifiers could be used to annotate artifacted segments.

To assess the degree of relationship between the parameters derived from the WND and CTR methods, the R2 of the linear regression was used. An error analysis could provide additional information. For example, a Bland-Altman plot would be informative to identify and provide further insight into the causes of those specific cases where a significant deviation is observed between the parameter calculated using the WND and CTR methods. In addition, the sample size is small and it would be necessary to expand the database and ensure the reproducibility of the experiment by obtaining multiple samples per subject and phase.

5 CONCLUSIONS

The IC-EHG technology has emerged as an alternative technique for analyzing myometrial electrophysiology in non-pregnant uteri. This technique allows for the exploration of spectral and non-linear parameters that have only previously been examined in pregnant uteri through EHG recordings on the abdominal surface. Two primary methodologies have been used in this context: CTR and WND analysis. This study aimed to investigate the relationship between parameters that characterize the same characteristics of the IC-EHG signal using CTR and WND analysis to assess their estimation without the need for cumbersome annotation of contractions.

In terms of the amplitude, the parameters from both methods are very highly correlated, indicating that the $envP80_{WND}$ parameter could be used to assess contraction intensity without prior segmentation, regardless of the menstrual cycle phase. Regarding the spectral content, associated to cell excitability, the MNF of uterine contractions can also be accurately inferred from whole window analysis, especially in MF and LL phases. Nonetheless, the signal complexity during contractions, associated to coordination among cells, would be poorly inferred without IC-EHG bursts identification.

Another important conclusion of this work is that, although longer recordings are necessary to reduce the possible variability between analysis windows, the optimal window size for these calculations is 2 minutes.

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