ARTICLE

Detection of impending reflex syncope by means of an integrated multisensor patch-type recorder

Antonella Groppelli[1,8], Martina Rafanelli[2,8], Giuseppe Dario Testa[2], Samuele Agusto[2], Giulia Rivasi[2], Erika Carbone[3], Davide Soranna[3], Antonella Zambon[3,4], Paolo Castiglioni[5,6], Andrea Ungar[2], Michele Brignole[1]✉ and Gianfranco Parati[1,7]

We assessed the capability of an integrated multisensory patch-type monitor (RootiRx®) in detecting episodes of reflex (pre)syncope induced by tilt table test (TTT). Firstly, we performed an intrapatient comparison of cuffless systolic blood pressure (SBP), R–R interval (RRI) and variability (power spectrum analysis) obtained by means of the RootiRx® with those obtained with conventional methods (CONV) with validated finger pressure devices at baseline in supine position and repeatedly during TTT in 32 patients affected by likely reflex syncope. Secondly, the LF/HF values obtained with RootiRx® during TTT were analyzed in 50 syncope patients. Compared with baseline supine recordings, during TTT a decrement of median SBP was observed with CONV (−53.5 mmHg) but not with RootiRx® ®(−1 mmHg). Conversely, RRI reduction (CONV: 102 ms; RootiRx®: 127 ms) and RRI Low Frequency/High Frequency powers ratio (LF/HF) increase (CONV: 1.6; RootiRx®: 2.5) were similar. The concordance was good for RRI (0.97 [95% CI 0.96–0.98]) and fair for LF/HF ratio (0.69 [95% CI 0.46-0.83]). During the first 5 min of TTT the LF/HF ratio was higher in patients who later developed syncope than in no-syncope patients. This ratio was significantly different among patients with syncope, presyncope or without symptoms at the time of syncope (p value = 0.02). In conclusion, cuffless RootiRx® was unable to detect rapid drops of SBP occurring during impending reflex syncope and thus cannot be used as a diagnostic tool for hypotensive syncope. On the other hand, RRI mean values and LF/HF power ratios obtained with RootiRx® were consistent with those simultaneously obtained using conventional methods.

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INTRODUCTION

Reflex (neurally mediated) syncope is the most frequent cause of transient loss of consciousness. Traditionally, reflex syncope is identified by its etiology and clinical presentation. Given that the efficacy of therapy is determined by the underlying mechanisms of syncope (either hypotensive or bradycardic phenotype) rather than by its etiology or clinical presentation, the careful assessment of these mechanisms is mandatory to provide patients with appropriate treatment [1]. Recent progress in technology now offers the possibility to characterize spontaneous (pre)syncopal events in daily life, thus improving our ability to identify hemodynamic patterns associated with reflex syncope. Indeed, syncope diagnosis might be improved through use of devices that allow for an integrated multisensor documentation of spontaneous events. The reliability of new technological devices in this setting, however, must be verified prior to their clinical use.

The purpose of this study was to assess the applicability and reliability of a new patch-type multisensor monitor (RootiRx®, Rooti Labs Ltd, Taipei, Taiwan) in detecting episodes of reflex (pre) syncope induced by tilt table test (TTT). Aim of our study was to explore the ability of this patch-type monitor to reliably measure the changes in systolic blood pressure (SBP) and the changes in in R–R interval (RRI) mean values and variability (power spectrum analysis) in such critical conditions.

METHODS

Firstly, we performed an intrapatient comparison of SBP, RRI mean values and variability [assessment of RRI spectral powers in the low frequency (LF, around 0.1 Hz) and High frequency (HF, around 0.3 Hz) and calculation of the LF/HF power ratio, considered to be an index of sympatho-vagal balance in RRI neural modulation [2] measured during TTT through RootiRx® and by means of a conventional continuous BP and HR monitoring methods (CONV), respectively. Secondly, we evaluated for each phase of TTT the difference in RRI mean values and spectral powers (including LF/HF powers ratio) measured by RootiRx® among patients who had syncope, presyncope or no event. The study was carried out at the Syncope Unit of San Luca Hospital, Istituto Auxologico Italiano, Milan, IT and at Azienda Ospedaliera Universitaria Careggi, Florence, IT. The study protocol was approved by the institutional review board of both Institutions. All participants provided a written informed consent.

Study design

The study group consisted of patients >18 years of age reporting a history of at least one syncope episode and undergoing TTT to confirm a suspicion

[1]IRCCS Istituto Auxologico Italiano, Faint & Fall programme, Cardiology Unit and Department of Cardiology, San Luca Hospital, Milan, Italy. [2]Syncope Unit, Division of Geriatric and Intensive Care Medicine, University of Florence and Azienda Ospedaliero Universitaria Careggi, Florence, Italy. [3]Biostatistics Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy. [4]Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy. [5]IRCCS Fondazione Don C. Gnocchi ONLUS, Milan, Italy. [6]Department of Biotechnology and Life sciences (DBSV), University of Insubria, Varese, Italy. [7]Department of Medicine and Surgery, University of Milano Bicocca, Milan, Italy. [8]These authors contributed equally: Antonella Groppelli, Martina Rafanelli ✉email: mbrignole@outlook.it

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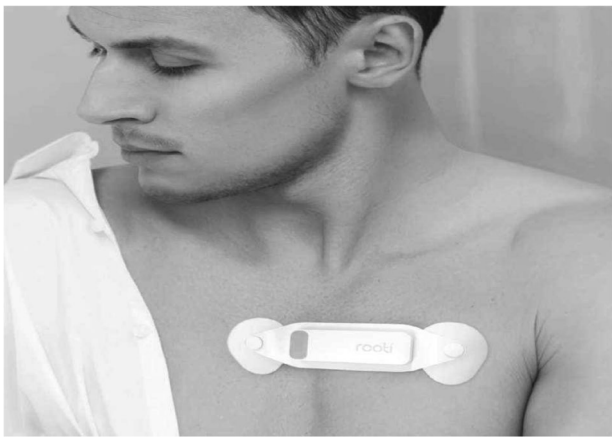

Fig. 1 The RootiRx. The RootiRx® multisensory patch-type system is a water-resistant compact ECG patch of 62 × 22 × 9 mm size and 14 g of weight. Published with permission from Rooti Labs Ltd.

of reflex syncope after exclusion of competing diagnoses. In particular, patients with likely cardiac syncope and those with a transient loss of consciousness of likely non-syncopal origin were excluded according to the diagnostic criteria of ESC guidelines [3]. TTT was performed according to the Italian protocol [4]. Positive TTT response was defined as the reproduction of spontaneous (pre)syncopal symptoms in the presence of a typical haemodynamic pattern. RootiRx® was applied to the patient chest before TTT. In addition, continuous ECG and finger beat-to-beat BP monitoring (Finometer®, Finapres Medical Systems, Enchede, The Netherlands or Task Force® monitor, CNSystem, Graz, Austria), was carried out during the whole test (CONV). In order to obtain comparable data between RootiRx® and CONV, continuous beat-to-beat data recorded by both methods were synchronized to the Internet exact time, extracted from these devices and stored on a PC. The analysis of stored data was made after the end of the test. Average RRI and SBP values were computed over 1-min time windows while RRI spectral powers and LF/HF powers ratio were estimated over 5 min time windows. This was done at baseline (following a 5-min rest period), 5 min after start of 60° head-up tilting, at the time of impending syncope [i.e., at the onset of presyncopal symptoms, but before the occurrence of complete loss of consciousness] or, alternatively, at the end of the upright tilt if symptoms did not occur, and finally during the recovery period (i.e., after returning to the supine position).

Description of the investigational device

The RootiRx® multisensory patch-type system is a water-resistant compact ECG patch of 62 × 22 × 9 mm size and 14 g of weight (Fig. 1). It is applied on the patient chest between the midsternal line and the left midclavicular line and around the third and fourth intercostal space and it is fixed on a disposable self-adhesive patch then connected to the skin with two electrodes. RootiRx® can make continuous ECG monitoring up to seven days at a sampling frequency of 250 Hz with 24-bit high resolution. Proprietary algorithms are used to analyze recorded data.

Cuff-less SBP is derived from the ECG signal. To estimate the ECG to BP transfer function, features are extracted from ECG waveform both in time and frequency domain. Based on statistical learning algorithm, a quality metric iterates and optimizes the model. A calibration mechanism provides personalized offset for each individual. More details are provided in [5].

The RootiRx® system uses the Lomb–Scargle method [6, 7] for spectral analysis of heart rate. This method allows analyzing irregularly sampled data without the need of interpolating and resampling evenly the time series. For this reason, the Lomb-Scargle periodogram is sometime preferred to the recommended spectral methods based on the fast Fourier Transform periodogram or autoregressive modeling [8]. However, the strong correlation between the sampling frequency of the tachogram and the corresponding heart rate value may influence he performances of this periodogram [9, 10]. Only RR intervals of sinus origin were used for the quantification of the mean RR interval and HRV parameters.

In addition to the above ECG-related parameters, RootiRx® is equipped with "passive sensors," such as 3-axis accelerometer, gyroscope, and magnetometer, like current smartphones [11]. In addition to information on activity and body position, data obtained with these sensors, in association with ECG data, can be analyzed to extrapolate information regarding respiratory function and sleep phases. These device features were not used for this study.

RootiRx® was tested in previous studies against a standard 12-lead Holter monitor [12] and 24-h ambulatory BP monitoring [5]. It has been used to assess heart rate variability [11] but it has never been compared against standard methods for the assessment of BP and RRI changes during TTT.

Description of the conventional methods for SBP and RRI monitoring during TTT

RRI and SBP were assessed by commercially available devices for continuous finger BP and ECG monitoring (Finometer®, Finapres Medical Systems, Enchede, The Netherlands, and Task Force® monitor, CNSystem, Graz, Austria), based on the photoplethysmographic volume clamp method [13, 14]. These devices are widely used in syncope facilities and are recommended as reference standard for BP monitoring during TTT by a recent consensus document [15]. RRI is derived by these devices from analysis of an integrated electrocardiographic signal. The Finapres device has been shown to provide reliable information on BP values and even more so on BP fluctuations as compared to intra-arterial recordings at rest and during tests known to induce fast changes in BP [16, 17]. The Task Force BP technology is similar to the CNAP® technology used and compared in critical care with intra-arterial recording [18]. In addition, the Task Force® monitor showed a good BP correlation with intra-arterial recording and other validated devices, including Finapres, and achieved the criteria for the "Quality Mark" (Gütesiegel) of the German Hypertension League [19].

The indices of cardiovascular autonomic regulation were obtained from analysis of RRI time series through power spectrum analysis techniques making use of a custom software [8, 20–22]. Briefly, during the off-line analysis performed after the test, our proprietary software (developed by the Milan group of coauthors) applies a derivative and threshold algorithm on the ECG to identify the R peak, with parabolic interpolation to refine the R wave fiducial point, and calculates the tachogram, i.e., the beat-by-beat series of R–R intervals (RRI). Premature beats and artifacts were identified visually and removed. The length of the tachogram has been set in 5-min frames, as a best compromise between the need for a large time series, in order to achieve greater accuracy in the computation, and the need to obtain stationary recordings, which would be easier for short time period recordings. The beat-by-beat series is then interpolated evenly at 5 Hz for fast Fourier Transform based spectral analysis. The power spectrum is calculated with the Welch's periodogram using 50% overlapped Hann data windows of 120 s length. Two major frequency components are quantified from the power spectrum: the high frequency (HF_{RR}) power, by considering spectral components between 0.15 Hz and 0.4 Hz, a recognized index of the vagal efferent modulation directed to the sinoatrial node [8], and the low frequency (LF_{RR}) power, by considering spectral component between 0.04 Hz and 0.15 Hz, which reflects sympathetic and vagal cardiac modulation. We also calculated the LF/HF ratio, a dimensionless index of cardiac sympatho-vagal balance [22, 23].

Statistical analysis and sample size

Continuous variables are shown as means ± standard deviations or medians (25th–75th percentile), in case of data not normally distributed. Normal distribution was assessed by the Shapiro–Wilk test and graphically with a Q-Q plot. Categorical variables are shown as frequency counts and percentages. The agreement among techniques in measuring the clinical variables (SBP, LF/HF, and RRI) was quantified by Lin's Concordance Correlation Coefficient (CCC) and relative 95% confidence interval using the U-statistics approach. This index was calculated in each phase of TTT test (supine pre-tilting, 5-min upright, symptoms or end upright and post tilting); the modified version of this index for repeated measurements was applied when considering all TTT phases jointly [24]. The differences in LF/HF ratio between the two approaches were also evaluated by a spaghetti plot. Finally, for each phase of the test, the Kruskal–Wallis test was performed to evaluate the difference in median values of LF/HF detected with the RootiRx® among 3 groups: syncope, presyncope, and no symptoms. All tests were considered two sided and a p value < 0.05 was considered statistically significant. The analysis was performed with the software R version 4.1.2.

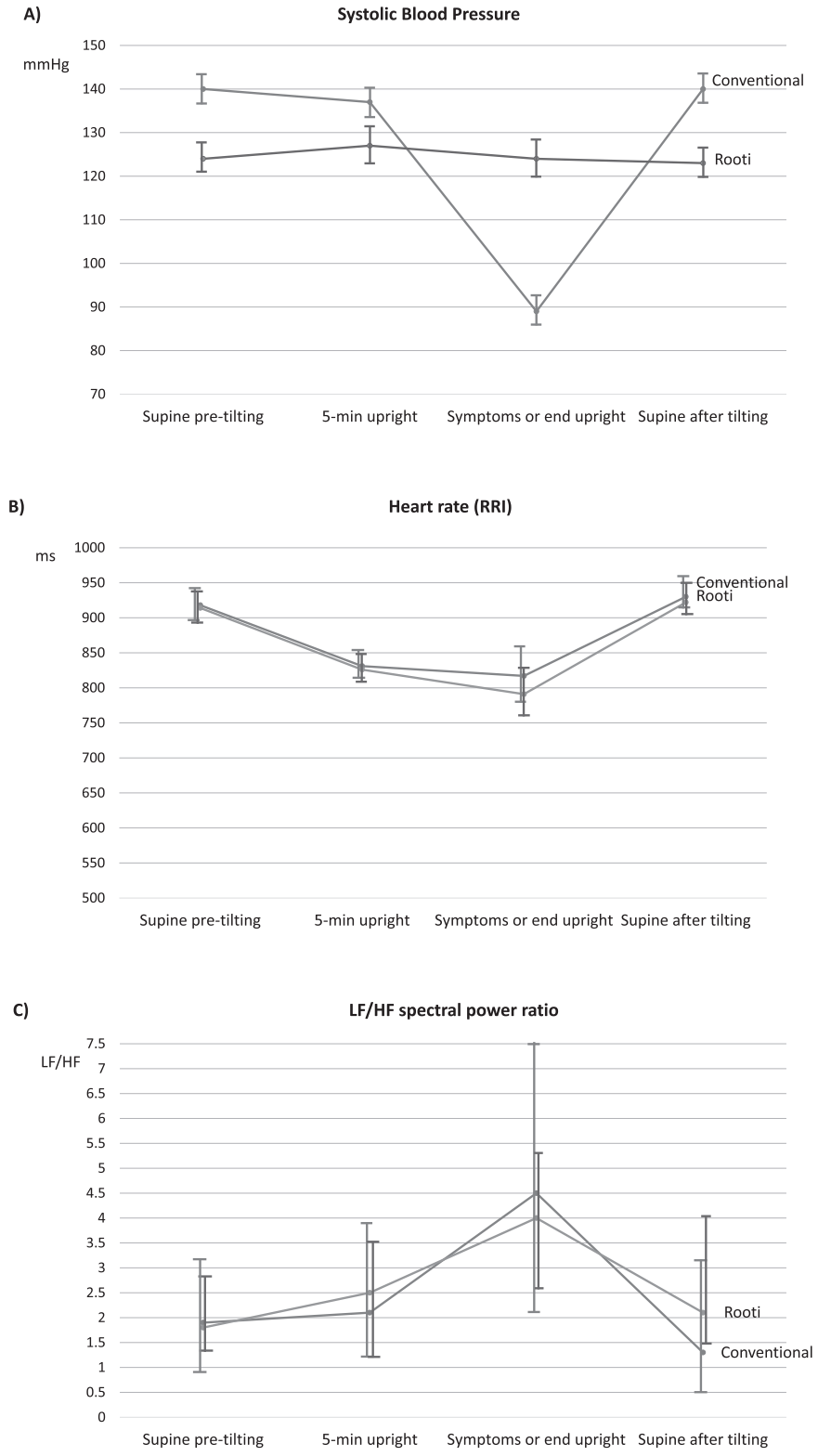

Fig. 2 Intrapatient comparison of systolic blood pressure (SBP), R-R interval (RRI) LF/HF spectral power between conventional and RootiRx methods. Values of SBP (mean ± SE), **A** R–R interval (RRI) (mean ± SE), **B** and RRI LF/HF spectral powers ratio (median; IQR), **C** for each phase of the TTT measured with RootiRx® and CONV, respectively, in 32 patients.

RESULTS

Intrapatient comparison

The intrapatient comparison between data provided by RootiRx® and by the conventional method was performed in 32 patients using the Finapres device; of these, 26 had a positive response during TTT. Their mean age was 57 ± 20 years and 17 (53%) were females. RootiRx® was unable to detect the drop in SBP that occurred at the time of symptoms (Fig. 2). Indeed, compared with baseline, at time of impending syncope, a decrement of SBP was observed with CONV (median: −53.5 mmHg; IQR: −78.2; −29.5)

Table 1. Comparison between CONV and RootiRx® estimates of SBP, and RRI mean values and LF/HF spectral powers ratio during TTT in 32 syncope patients.

Period	CONV	RootiRx®	CCC[a] (95% CI)
Supine pre-tilting			
-SBP Mean ± SD, mmHg	140 ± 20	124 ± 19	0.48 (0.35–0.59)
-RRI Mean ± SD, ms	918 ± 143	914 ± 150	0.99 (0.98–0.99)
-LF/HF Median (IQR)	1.9 (0.8–3.2)	1.8 (1.4–2.8)	0.50 (0.30–0.66)
5-min upright			
-SBP, mmHg	137 ± 19	127 ± 21	0.66 (0.44–0.81)
-RRI, ms	831 ± 129	826 ± 135	0.99 (0.97–0.99)
-LF/HF (IQR)	2.1 (1.2–3.9)	2.5 (1.2–3.5)	0.91 (0.77–0.96)
Symptoms or end upright			
-SBP, mmHg	89 ± 19	124 ± 20	0.04 (−0.11 to 0.18)
-RRI, ms	817 ± 234	791 ± 208	0.97 (0.95–0.98)
-LF/HF (IQR)	4.5 (2.1–7.5)	4.0 (2.6 – 5.3)	0.61 (0.24–0.82)
Supine after tilting			
-SBP, mmHg	140 ± 18	123 ± 19	0.25 (0.04–0.44)
-RRI, ms	930 ± 136	922 ± 132	0.93 (0.85–0.97)
-LF/HF (IQR)	1.4 (0.6–3.1)	2.1 (1.5–4.0)	0.70 (0.50–0.83)

For such comparison, all patients used the Finapres device.
[a]According to Landis and Koch scale, the CCC agreement is almost perfect between 0.81 and 1.00, substantial between 0.61 and 0.80, moderate between 0.41 and 0.60, fair between 0.21 and 0.40, slight between 0.01 and 0.20.
SBP systolic blood pressure, *RRI* R–R interval, *LF* low frequency powers, *HF* high frequency powers, *CCC* Lin's Concordance Correlation Coefficient.

while SBP estimated by RootiRx®remained unchanged (median: -1 mmHg; IQR: −10; 9.5). Conversely, RRI decreased with both techniques (CONV: median: −102 ms IQR: 10; 238; RootiRx®: median: −127 ms; IQR: 20; 231). Finally, also the LF/HF ratio increased with both techniques in the initial TTT phases (CONV: median: 1.6; IQR: 0.2; 4.6; RootiRx®: median: 2.5; IQR: 1.0; 3.8). For each TTT phase the concordance correlation coefficient (CCC) between CONV and RootiRx® is reported in Table 1 and in Figs. 1S, 2S, 3S and 4S included in the supplemental file. Low CCC values were observed in all phases for SBP, while higher CCC values characterized RRI. The CCC of LF/HF varied from 0.50 for supine pre-tilting phase to 0.91 for 5-min upright phase.

Finally, we estimated the total CCC throughout all TTT phases and observed poor concordance for SBP (0.29 [95% CI 0.16–0.41]), good concordance for RRI (0.97 [95% CI 0.96–0.98]) and fair agreement for LF/HF ratio (0.69 [95% CI 0.46–0.83]). The latter increased to 0.72 when deleting two patients showing extreme values as highlighted by the graphical representation of individual differences between RootiRx® and CONV (Fig. 3).

TTT response and LF/HF patterns

A total of 50 syncope patients applied the RootiRx® patch and underwent TTT; their mean age was 61 ± 19 years and 27 (54%) were females. TTT was positive in 35 (70%) patients: presyncope was induced in 27 patients and syncope in the 8 patients who had a more rapid and a greater vasovagal effect causing complete loss of consciousness before tilt down. Reliable data on RRI, and LF/HF were obtained in all patients with RootiRx®. The LF/HF obtained with RootiRx® during TTT was significantly different among patients with syncope, presyncope or without symptoms only at the time of syncope (Kruskal–Wallis test p value = 0.02) (Fig. 4). Median and interquartile range are reported in Table 1S in the supplemental files.

DISCUSSION

Cuff-less RootiRx® was unable to detect rapid drops of SBP as those occurring at the time of impending reflex syncope. Thus, SBP monitoring by RootiRx® cannot be used as a diagnostic tool for hypotensive syncope. Conversely, RootiRx® might be a valuable tool for long-term monitoring of cardiac autonomic modulation in patients with reflex syncope given the good correlation of mean values and changes of RRI and LF/HF ratio estimated with RootiRx® with those simultaneously obtained through conventional method.

There is a continuously increasing number of wearable devices, most of which based on cuffless machine-learning technologies, which are being proposed for clinical application. However, these approaches are still currently based on immature technologies which need further improvement and proper validation before being considered reliable for clinical use [24, 25]. Non-invasive blood pressure estimation from ECG, based on machine-learning techniques—similar to that of RootiRx®—has been previously evaluated at rest against cuff oscillometric BP measurements [26]; the mean absolute error was 8.6 ± 10.7 mmHg for SBP and 18.2 ± 8.4 mmHg for diastolic blood pressure. Cuff-less RootiRx® has also been evaluated against 24-h oscillometric ambulatory BP monitoring in 84 subjects [5]. Mean 24-h SBP by RootiRx® was higher than that observed with a validated oscillometric device: (131.1 ± 15.9 mmHg versus 125.4 ± 10.9 mmHg respectively) with a moderate degree of agreement (correlation coefficient r = 58) and a grade C between-device difference according to the American National Standards Institute, Inc/Association for the Advancement of Medical Instrumentation/International Organization for Standardization (ANSI/AAMI/ISO) [27]. This difference, observed in outpatient hypertensive subjects, was enhanced at low SBP values, such as those occurring at the time of impending syncope in the present study, making SBP estimates by RootiRx® unreliable in this clinical condition. Rivasi et al. [28] have recently found that some patients with reflex syncope have drops of systolic SBP below an absolute value of 100 mmHg during 24-h ambulatory BP monitoring, not present in a control group of non-syncopal patients, reflecting a feature of vasovagal syncope. Thus, the RootiRx® is probably unable to discover such new important diagnostic finding.

RootiRx® has also been used to assess heart rate variability [29] but it has never been compared against conventional methods

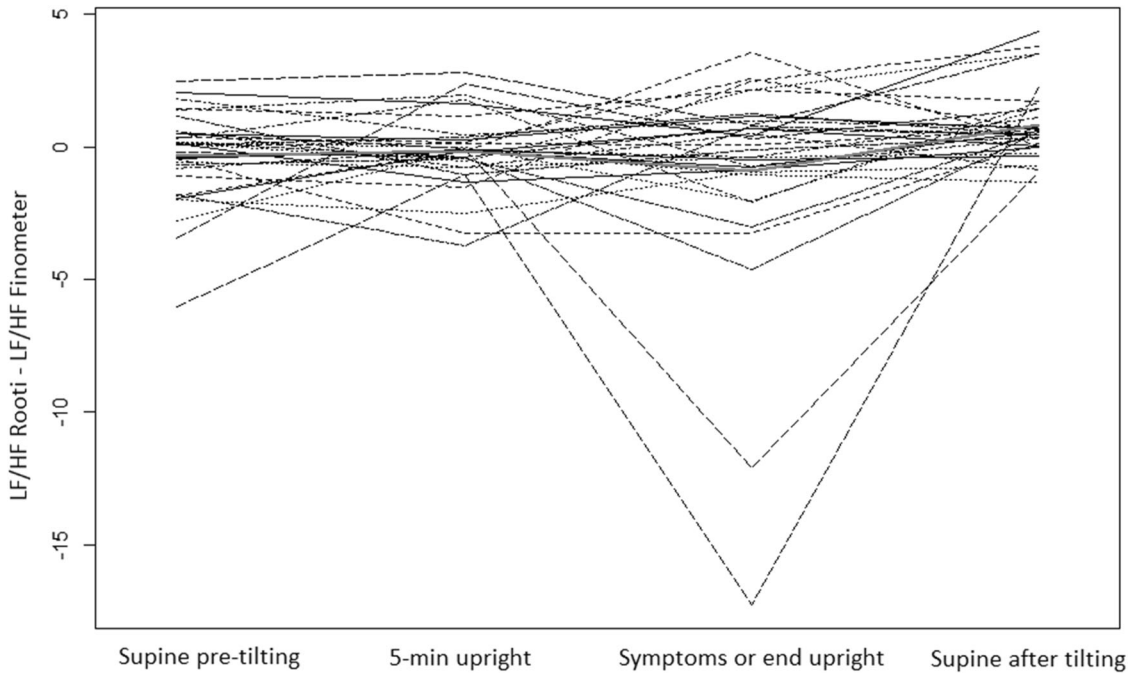

Fig. 3 Spaghetti plot of differences in LF/HF ratio between RootiRx® and CONV. For each individual the difference in LF/HF values between the two measuring instruments was calculated. The responses for the same individual over the different test phases are connected by lines to show the individual-wise trends. The 4 test phases are reported on the x-axis, the differences in LF/HF estimates provided by the two methods are reported on y-axis. The red line shows the trend of the mean of between-method differences over the 4 test phases calculated with a model for repeated measurements with an unstructured covariance matrix. Two individuals showed an extremely high value of LF/HF ratio at the time of symptoms with CONV method, suggesting a likely technical error.

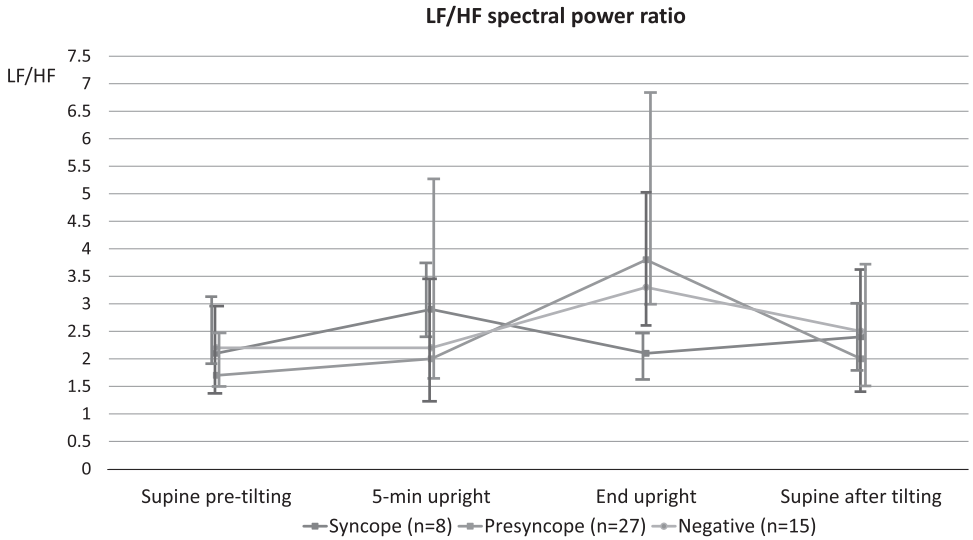

Fig. 4 LF/HF patterns obtained with RootiRx® according to TTT results in 50 syncope patients. Values are expressed as median with their interquartile range.

during TTT. In our study, the substantial agreement of LF/HF ratio values estimated by RootiRx® with those obtained through the conventional approach making use of a classic method for power spectral analysis [20–23] suggests that long-term monitoring of cardiac autonomic modulation by RootiRx® is potentially feasible for the study of the autonomic profile of patients with reflex syncope. Frequency domain measurements RRI variability, in particular estimates of RRI LF/HF ratio, have been assessed during TTT in patients with syncope and in controls by several authors in the past, with conflicting results [24, 30–34]. In general, most studies found an increase of RRI LF/HF ratio in response to upright tilting, which is consistent with the known compensatory increase of sympathetic cardiac modulation (Fig. 2). In the patients of our study who developed syncope, this increase occurred earlier and disappeared at the time of presyncope and syncope suggesting the onset of vagal hyperactivity at the time of impending syncope (Fig. 4). This suggests that different changes in cardiac autonomic modulation occur during different TTT phases in patients with syncope and in those with presyncope, and that assessment of RRI LF/HF ratio can help identifying these differences.

Future directions

Our study provides evidence supporting clinical application of the RRI mean values and variability (in particular of LF/HF power ratio) estimates provided by RootiRx®. In addition to these estimates, however, the multisensor patch-type recorder RootiRx® has the capability to also record other parameters that might be potentially useful for identifying a predisposition to reflex syncope, such as physical activity, body position and movements, respiratory frequency and body surface temperature. Additional studies are needed to clarify whether the combination of these additional parameters with RRI and BP monitoring might help to better define a specific pattern (phenotype) characterizing patients who have susceptibility to reflex syncope.

SUMMARY

What is known about this topic

- There is a continuously increasing number of wearable devices aimed at continuous blood pressure and heart rate measurement, most of which based on cuffless machine-learning technologies, which are being proposed for clinical application.
- Recent progress in technology now offers the possibility to characterize spontaneous (pre)syncopal events in daily life, thus improving our ability to identify hemodynamic patterns associated with reflex syncope.
- The reliability of new technological devices in this setting, however, must be verified prior to their clinical use in critical situations of hypotension

What this study adds

- The purpose of this study was to assess the applicability and reliability of a new patch-type multisensor monitor (RootiRx®, Rooti Labs Ltd, Taipei, Taiwan) to reliably measure the changes in systolic blood pressure and the changes in in R–R interval mean values and variability (power spectrum analysis) in a critical condition such during impending reflex syncope.
- Cuff-less RootiRx® was unable to detect rapid drops of systolic blood pressure. Thus, it cannot be used as a diagnostic tool for hypotensive syncope. Conversely, mean values and changes of RRI and LF/HF ratio were consistent with those simultaneously obtained through conventional methods.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available upon reasonable request https://zenodo.org/badge/DOI/10.5281/zenodo.7793208.svg

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AUTHOR CONTRIBUTIONS

MB, GFP and AU designed the study and wrote the text. AG and MR designed the CRF and the database, recruited the patients, and acquired the data. GDT, SA, and GR recruited the patients, and acquired the data. EC, DS, AZ, and PC performed statistical analysis and methodology of the study. All authors contributed to the discussion of results and to the revision of the text.

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COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Michele Brignole.

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