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Complete List of Authors:	Le Guen, Morgan; Hopital Foch, Department of Anesthesiology Squara, Pierre; Clinique Ambroise Pare, ICU Ma, Sabrina; Hopital Foch, Department of Anesthesiology Adjavon, Shérifa; Hopital Foch, Department of Anesthesiology Trillat, Bernard; Hôpital Foch, Department of Information Systems Merzoug, Messaouda; Clinique Ambroise Pare, Research Unit Aegerter, Philippe; GIRCI-IdF, 75019 Paris, France, Methodology Unit; Paris-Saclay University, UVSQ, INSERM, , U1018 (Center for Epidemiology and Population Health) Fischler, Marc; Hopital Foch, Anesthesia
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PATCH-VALIDATION: A PROTOCOL FOR THE EVALUATION OF A MULTIVARIABLE WEARABLE SENSOR IN A COHORT OF ANAESTHETISED PATIENTS

Abbreviated title: Validation of a multivariable wearable sensor

Morgan Le Guen,[1] Pierre Squara,[2] Sabrina Ma,[1] Sherifa Adjavon,[1] Bernard Trillat,[3] Messaouda Merzoug,[2] Philippe Aegerter,[4] Marc Fischler[1]

Author affiliations

[1] Hôpital Foch, Department of Anaesthesiology, 92150 Suresnes, France, and Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

[2] Research Unit, Centre Médico-Chirurgical Ambroise Paré, 92200 Neuilly-sur-Seine, France

[3] Hôpital Foch, Department of Information Systems, 92150 Suresnes, France

[4] Methodology Unit, GIRCI-IdF, 75019 Paris, France, and U1018 (Center for Epidemiology and Population Health), Paris-Saclay University, UVSQ, INSERM, 94807, Villejuif, France

Corresponding Author: Marc Fischler, MD, Department of Anaesthesiology, Hospital Foch, 40 rue Worth, 92150 Suresnes, France. E-mail: m.fischler@orange.fr

Phone: 0033 1 46 25 24 42 (Business telephone) – 0033 6 09 68 78 54 (Mobile).

Fax: 0033 1 46 25 240 88

Contact information for the trial sponsor: Pierre Squara, Research Unit, Centre Médico-Chirurgical Ambroise Paré, Neuilly-sur-Seine, France. E-mail: pierre.squara@orange.fr.

Role: study design; collection, management, analysis, and interpretation of data; writing of the report

Key words: telemedicine; adult anaesthesia; adult intensive and critical care; surgery

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ABSTRACT

Introduction: Except for intensive care units, where the monitoring of vital signs is continuous, intermittent care is standard practice. However, at a time when only the patients with the most serious conditions are hospitalised and only a fraction of these patients are in intensive care units, this type of monitoring is no longer sufficient. Wireless monitoring has been proposed, but it requires rigorous validation. The aim of this study is to compare vital signs obtained from a precordial patch sensor to those obtained with conventional monitoring.

Methods and analysis: The patch-validation trial will be an observational, prospective, single-centre open study of 115 adult anaesthetised patients monitored with both a wireless sensor (myAngel VitalSigns™, Devinnova, 34080 Montpellier, France) and a standard bedside monitor (Carescape Monitor B850, General Electric Healthcare, Chicago, Illinois). Both sensors will be used to record values of peripheral oxygen saturation, respiratory rate, heart rate, body temperature, and blood pressure (systolic, diastolic). The main objective will be to assess the level of agreement between the two systems during the patients' stay in the post-anaesthesia care unit from a metrological or a clinical point of view. The secondary objectives will be to assess the same parameters under anaesthesia, the frequency of missing data or artefacts, the diagnostic performance of the systems, ~~the~~ adverse events and the acceptability of the patch by the patient. Bland-Altman plots will be used in the main analysis to detect discrepancies and estimate the limits of agreement.

Ethics and dissemination: Ethics approval was obtained from the Ethical Committee (Toulouse, France) on April 10, 2020. We are not yet recruiting subjects for this study. The results will be submitted for publication in peer-reviewed journals. The trial registration number is as follows: ClinicalTrials.gov (NCT04344093).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to validate a new multivariable wearable sensor in patients when they are under anaesthesia and in the post-anaesthesia care unit, which are times at which artefacts in signals are prevalent.
- The study results will help determine the level of agreement between the parameters collected by a conventional monitor and the patch (in particular, blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature).
- The study results will help estimate the frequency of artefacts and determine the acceptability of this patch by patients during their stay in the post-anaesthesia care unit.
- A limitation of this study is that we will compare only minute-by-minute data.

INTRODUCTION

Although some surgical patients with severe comorbidities or complications are hospitalised in units with a high level of monitoring, most patients are hospitalised in conventional units where clinical supervision is infrequent, particularly during the night.[1]

Adverse events are particularly frequent after surgery, as shown by a prospective international 7-day cohort study of outcomes following elective adult inpatient surgery in 44 814 patients in 27 countries. A total of 7 508 patients (16.8%) developed one or more postoperative complications, and 207 patients (0.5%) died.[2] Hospital costs are significantly increased by these complications,[3] which largely occur due to the inability to quickly detect a significant worsening of a patient's condition.[4]

To improve nurses' skills in assessing a patient's clinical situation, the Early Warning Score (EWS) has been introduced and is measured repeatedly. This score initially included five physiological parameters: heart rate, systolic blood pressure, respiratory rate, temperature and consciousness level.[5] Many variants that include additional variables, such as oxygen saturation, urine output, and clinical signs of deterioration (pallor, sweating, looking unwell), have been proposed. NHS England promoted the adoption of the National Early Warning Score 2 (NEWS2) for adult patients by March 2019.[6 7] However, studies have shown contradictory results regarding the added value of the EWS in relation to patient outcomes.[8-10]

Alternatively, the clinical evaluation of nurses can be augmented or substituted by devices that allow the continuous monitoring of vital signs. Thus, Philips General Care Solutions proposed an automated Modified Early Warning Score (MEWS) system, the Philips IntelliVue Guardian Solution (Guardian),[11] and, concerning wearable vital sign monitoring devices, Weenk et al. showed that ViSi Mobile and HealthPatch, give more frequent alerts than do nurses.[12] Michard et al. reviewed numerous innovations, particularly those designed to detect respiratory complications using wearable and wireless sensors.[13] Before new sensors can be used, their accuracy and reliability must be verified.[14 15] The point of validation is of great importance since the general public can buy lay-user devices that seem similar but do not yield good quality results. Thus, Gillinov et al. compared five optic heart rate monitors during various types of aerobic exercise and showed large differences between the monitors and a reference (an electrocardiograph device).[16] Van Lier et al. recently reported at least three major

reasons for inadequate validation (the use of different and sometimes inappropriate statistical methods, the evaluation of different levels for each parameter, and a lack of criteria to determine validity) and recently published a standardized protocol for assessing the validity of physiological signals from wearable technology.[17] We have focused our interest on a new device, the myAngel VitalSigns™ (VS), which is a multisensory medical device including three electrocardiography (ECG) leads and sensors that can measure physiological parameters such as blood pressure, heart rate, respiratory rate, peripheral oxygen saturation (SpO_2), actimetry, posture and body temperature. Our goal is to evaluate this device during patients' stay in the post-anaesthesia care unit (PACU), where patients' movements can generate artefacts (main objective), and during their surgical procedure, where electrocautery and electronic devices can also create artefacts (one of the secondary objectives).

.

METHODS AND ANALYSIS

Trial design

This is a prospective observational study that will be conducted in an academic hospital in which all types of surgical procedures, with the exception of cardiac and orthopaedic procedures, are performed. The study has not yet recruited patients. They will be consecutively enrolled and followed up for their entire stay in the operating room and the PACU.

Participant eligibility and consent

Patients will be included if they meet all of the following criteria: (1) are over 18 and under 85 years of age, (2) will require general anaesthesia for extra-thoracic surgery, (3) will be in the supine position during surgery, and (4) have provided written informed consent. The exclusion criterion was pregnancy.

The studied device

The VS medical device, which has not yet obtained CE or FDA approval, comprises a reusable electronic module, which allows physiological data to be acquired, and a disposable skin patch, which ensures three contact electrodes (Figure 1; Devinnova, 34080 Montpellier, France). Sensors integrated into the electronic module allow the measurement of the following vital parameters: 3-lead ECG signals, oxygen saturation, respiratory rate, heart rate, body temperature, blood pressure (systolic, diastolic), actimetry (distance travelled, speed, number of steps, posture), and abrupt change in position (impacts, falls). The electrodes enable signals at the three ECG leads to be measured (DI, aVL, and aVR). The patch sensor also includes a dry zinc/air battery (button battery 1.4 V, 900 mah), which powers the electronic module and makes the medical device functional for up to 5 days.

The heart rate measurements are based on the detection of R peaks and allows RR intervals to be analysed. Blood pressure is determined from the pulse transit time, and is calculated by proprietary and artificial intelligence methods.[18-20] Respiratory rate is measured from a pressure sensor that evaluates the variation in chest signal amplitude from a sealed chamber at a constant pressure. Oxygen saturation is measured by an

infrared transceiver that maintains constant and homogeneous contact at the emitted wavelength; the reflection measurements make this method reproducible and reliable.[21] The temperature is measured by infrared spectroscopy, which also has high reproducibility over time. A 6-axis accelerometer is used to evaluate the gravitational effect, i.e., a patient's postural position (lying down, right or left flank, standing, sitting, immobile, moving) as well as the actimetry (number of steps, distance covered, speed) if he or she falls. The patch is waterproof, and its size is appropriate for daily use.

A mobile device (smartphone with 3G/4G connection, tablet with internet connection, etc.), with Android (version 4.3 or newer) or iOS (version 10.0 or newer), allows the electronic module to be configured and declarative information of the patient to associate him with the medical device. After this configuration all data will be recorded and sent to the mobile device via Bluetooth Low Energy (BLE V4.0 or higher).

The data acquired by the electronic module are stored in the VS medical device and transmitted to the mobile device, which will encrypt and transfer the data in real time to a dedicated certified health server. The information stored in the medical device itself is also encrypted and is recorded in a local memory operating system in a first-in, first-out (FIFO) manner when the BLE link is maintained. When there is no BLE link between the VS device and the mobile (due to empty batteries or unpaired devices) the VS stores the data in its internal memory and automatically repeats the BLE pairing process (via a thread) with the mobile device until it succeeds. The memory of the VS can store data for up to 4 days. When pairing is again operational, the data acquired in real time are transmitted again and become visible on the mobile device (priority data); the data stored in the memory of the VS (resulting from the link break) are parallelized (via a thread) and sent directly to the buffer zone of the mobile device before being transferred to the certified health server.

Data can be seen in real-time using the connection between the mobile device and VS and *a posteriori* from the cloud server.

Intervention

The skin patch is placed on the lower part of the sternum (Figure 1).

All recorded data will include an absolute timestamp, where the mobile device is the reference.

Anaesthesia will be induced following a standard protocol and monitoring, including electrocardiography, non-invasive arterial blood pressure, pulse oximetry, capnography, and inspiratory and expiratory sevoflurane concentration measurements, and train of four monitoring (Aisys anaesthesia machine, Carescape Monitor B850, General Electric Healthcare, Chicago, Illinois, USA). All patients will be transferred after surgery to the PACU, where usual automated monitoring (electrocardiogram, non-invasive arterial blood pressure, pulse oximetry) will be performed and treatment will be administered.

The study will end when the patient leaves the PACU and returns to the surgical ward.

Data collection

Demographic data, including age, sex, American Society of Anaesthesiologists classification, body mass index, underlying diseases, reason for the surgical procedure, and type of surgical procedure, will be collected upon inclusion in the study.

All intraoperative monitoring variables (blood pressure, heart rate, pulse oximetry, ventilatory variables, including tidal volume, ventilator frequency, peak and mean airway pressures, and partial tension of end-tidal carbon dioxide pressure) will be collected using Centricity Anaesthesia® with one value per minute. This system is an anaesthesia information management system that automatically collects and stores data in a repository, which can be subsequently exported as a spreadsheet file (GE Healthcare, Buc, France). All variables monitored in the PACU (blood pressure, heart rate, pulse oximetry, respiratory rate) will also be collected using Centricity Anaesthesia with one value per minute, except for arterial pressure, which is measured at a higher frequency (from one measurement per minute to one every 15 minutes according the clinical state of the patient). The data from the patch sensor will not be communicated to the anaesthesiologists or to the nurses and other health care providers during the study period.

Because the main goal of this study is to investigate how postoperative physiological changes can be monitored with the patch, notes about any relevant findings will be made during the study. For example, if a complication occurs, it will be noted with the corresponding date and time and be linked with the corresponding measurements.

Finally, when a nurse removes the patch, he/she will assess the status of the skin: healthy skin (stage 0), redness limited to the contact area between the device and the skin (stage 1), redness extending beyond the contact surface of the device (stage 2), and the appearance of blisters (stage 3). The patient will be asked to evaluate his or her acceptance of the sensor using a 4-point Likert scale (from 0 = intolerable to 4 = no problem at all).

Outcomes measures

Following the van Lier proposal,[17] the validity of the wearable device will be assessed at three levels: (1) the raw signal level; (2) the clinical parameter level; and (3) the clinical event level, with the detection of relevant physiological changes. The main objective is to determine the level of agreement between the parameters collected by the conventional monitor and the patch sensor (blood pressure, heart rate, respiratory rate, oxygen saturation) during patients' stay in the PACU.

The secondary objectives are 1) to determine the level of agreement of the measured parameters during surgery in the operating room, 2) to determine the frequency of artefacts and blank/null outputs from the wearable device and, more globally, the signal-level validity, 3) to estimate the diagnostic performance of the patch sensor at the event level and 4) to determine the acceptability of this patch by patients during their stay in the PACU.

Statistical analysis

Number of patients to be included

The aim of this study is to test the equivalence of two devices in recording the same data for the same patients. There is no standard method for the analysis of discrete time series (raw signal level). Therefore, an approach based on the quality of physiological data recorded (clinical parameter level) was used to calculate the required number of patients.

For heart rate equipment, the recommendations for the limits of acceptable error are a difference of 5 beats per minute (bpm) or 10%, whichever is greater, between the device of interest and a reference device, as proposed by the Association for Advancement of Medical Instrumentation in 2002.[22] We then adopted these relative limits for all parameters. We extracted possible values for the distribution of differences between a patch and a reference sensor from the papers of Smolle,[23] Breteler[24] and van Lier.[17] Two methods are considered to be in

agreement when a predefined maximum allowed difference (Δ) is larger than the higher observed limit of agreement (LoA) and -Δ is smaller than the lower LoA. The 95% confidence interval (CI) of the LoA must be taken into account for proper interpretation, and to be 95% certain that the methods do not disagree, Δ must be larger than the upper 95% CI limit of the higher LoA and -Δ must be smaller than the lower 95% CI limit of the lower LoA. We then followed the new method proposed by Lu et al. that takes power into account.[25] Thus, considering a standard deviation of difference in heart rate of 4 bpm, a limit of acceptable error of 10 bpm (roughly 10%), a two-sided alpha risk of 5% and a 90% power, a sample of 136 pairs of measures are required. If two measures (m=2) of the same parameter are sampled on the same patient by two devices instead of one, the inclusion of n patients would yield 2n pairs of measures; however, taking into account the intra-patient correlation r, which is usually estimated to be 0.5, the design effect (DE) is 1+ (m-1)r = 1.5. Thus, the non-independence of observations within the same patient requires 1.5 * 2 * n paired measures to obtain the same amount of information as that given by one pair of a measure for each of 2*n independent patients. Therefore, 136 independent pairs being required indicates that 136/1.5 = 90 patients need to be measured on two occasions by the two devices being assessed. If 3 measurements (m=3) are considered, then DE=2, and 68 patients should be measured on three occasions.

Taking into account that approximately 20% of the data may be unusable, it is anticipated that 115 patients need to be included in the study to ensure that the data of 90 patients (with two paired measurements, each in the post-operative period) can be analysed.

Detection of artefacts

A value will be automatically considered to be an artefact if it is outside one of the "normal" ranges defined in previous studies: 1) a value that is > 50% different from the previous value, unless it is followed by a value equal to ± 25%; or 2) a value that is out of the physiologically plausible range (heart rate < 5 or > 250 bpm, systolic artery pressure < 20 mm Hg or > 300 mm Hg or less than diastolic pressure plus 5 mm Hg, diastolic artery pressure < 5 mm Hg or > 225 mm Hg, SpO_2 modification ≥ 8% between two consecutive measurements, respiratory rate < 3 or > 125 breaths per minute, skin temperature modification of ≥ 1° between two consecutive measurements). Furthermore, two clinicians will independently review all data in graphical form (one

graph/variable/patient) before and after the artefacts are automatically identified. A third clinician will also review the data when there is discordance.

The selected rules to define artefacts may be updated according to the experience. The successive rules will be recorded in a register and all recordings will be reviewed in the light of these new rules.

Statistical analyses of reliability and agreement

Descriptive summaries will be provided for each parameter and for each device. For continuous variables, the mean, median and their 95% confidence limits, obtained using bootstrapping, will be provided. For discrete variables, counts, percentages and confidence limits, obtained using bootstrapping, will be provided. The relative frequency of the data gap and artefacts for each parameter will be given as a percentage of the total number of measurement points and of observations, respectively, with the corresponding 95% CI. The delay (hours) to the first occurrence of data loss or end of service of the devices will be described and analysed with Kaplan-Meier survival curves.

At the signal level, cross-correlation will be used to compare the wearable device to a reference along the time series for each participant and each signal. When the cross-correlation coefficient is larger than 0.8 for all participants, the level of agreement is deemed acceptable, and the assessment is completed by calculating the differences.

At the parameter level, Bland-Altman analysis for repeated measurements, which accounts for multiple observations per individual, will be performed to create mean-difference plots and compare the accuracy or bias (mean difference), precision (standard deviation of difference), and the LoAs that are expected to contain 95% of paired differences between the measurements taken by the two methods, and their CIs, with those reported in the literature. A generalized linear mixed model (GLMM) will be used to calculate the components of variance, notably the within-subject variation, to correct the variance of differences.[26] If the 95% CI for the 95% LoAs are within the predefined agreement limits, which are clinically acceptable, the two methods are considered to have sufficient agreement to fulfil the agreement requirements.

In addition, a Clarke error grid analysis, with standard predetermined grids for heart rate, respiratory rate, artery pressure, SpO_2, and temperature, will be conducted to identify the consequences of clinical decisions.[27]

For adverse events, such as bradycardia, the sensitivity and specificity of the wearable device compared with the reference sensor will be calculated with 95% Cis.

Data from the post-operative period and from the intraoperative period will be analysed separately.

A two-tailed p value < 0.05 will be considered statistically significant, without any adjustment for multiplicity.

All statistical analyses will be performed using R software (version 3.2.4).

Missing values

Missing data will not be replaced.

Data registration

Data will be entered into the eCRF by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF, the trial database will be established. The data collection process will be monitored by trained research coordinators.

Patient withdrawal

Any participant who wishes to terminate his/her participation in the study can withdraw from the trial at any time without the need for further explanation. Participants who withdraw from the study will be followed up according to routine clinical practice.

Safety

Every serious adverse event (SAE) related to the studied procedure, regardless of whether it was expected, will be reported within 24 hours by the investigator to the sponsor on a SAE form on which the date of occurrence, criterion of severity, intensity, relationship with the study evaluated and the outcome will be indicated. The period in which SAE should be reported begins from the day of written informed consent is obtained to the end of the follow-up period. Whenever a SAE persists at the end of the study, the investigator will follow the patient until the event is considered resolved. The management of serious adverse events will follow regulations and good clinical practices.

Data handling and retention

The data will be handled according to French laws under the responsibility of the Research Unit, Centre Médico-Chirurgical Ambroise Paré (Neuilly-sur-Seine, France). All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The cleaned and frozen trial database files will be anonymised and stored for 15 years.

Patient and public involvement

Patients and the public will not be involved in any of the phase of this study.

Limitations

A limitation of this study is that we will compare only minute-by-minute data. More sophisticated technologies for the detection of artefacts in monitoring trends in intensive care that can be used are as follows: (1) the Rosner statistic; (2) slope detection with rules; and (3) comparisons with a running median (median detection).[28]

ETHICS AND DISSEMINATION

Ethics

Ethics approval was obtained for the Patch-Validation trial from the Ethical Committee (Toulouse, France) on April 10, 2020. Written informed consent is required from patients prior to their participation in the study. The patch-validation trial is registered at ClinicalTrials.gov with the trial identification number NCT04344093.

We are not yet recruiting subjects for this study.

Dissemination

The Standard Protocol Items and Recommendations for Interventional Trials will be followed.

Publication plan

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the approval of the principal investigators and the methodologist.

The co-authors of the report and publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. The international recommendations for authorship will be followed.

REFERENCES

1. Churpek MM, Edelson DP, Lee JY, *et al.* Association Between Survival and Time of Day for Rapid Response Team Calls in a National Registry. *Crit Care Med* 2017;45:1677-82.

2. International Surgical Outcomes Study g. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016;117:601-09.

3. Michard F, Mountford WK, Krukas MR, *et al.* Potential return on investment for implementation of perioperative goal-directed fluid therapy in major surgery: a nationwide database study. *Perioper Med (Lond)* 2015;4:11.

4. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med* 2009;361:1368-75.

5. Morgan RJM, Williams F, Wright M. An early warning scoring system for detecting developing critical illness. *Clin Intensive Care* 1997;8:100.

6. Retrieved from https://improvement.nhs.uk/documents/3657/Resources_to_support_the_adoption_of_NEWSFINAL.PDF.

7. Retrieved from https://www.england.nhs.uk/ourwork/clinical-policy/sepsis/nationalearlywarningscore/news-frequently-asked-questions/#4-why-has-a-news2-been-launched.

8. McGaughey J, Alderdice F, Fowler R, *et al.* Outreach and Early Warning Systems (EWS) for the prevention of intensive care admission and death of critically ill adult patients on general hospital wards. *Cochrane Database Syst Rev* 2007:CD005529.

9. Alam N, Hobbelink EL, van Tienhoven AJ, *et al.* The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. *Resuscitation* 2014;85:587-94.

10. Shamout F, Zhu T, Clifton L, *et al.* Early warning score adjusted for age to predict the composite outcome of mortality, cardiac arrest or unplanned intensive care unit admission using observational vital-sign data: a multicentre development and validation. *BMJ Open* 2019;9:e033301.

11. Mestrom E, De Bie A, Steeg MV*, et al.* Implementation of an automated early warning scoring system in a surgical ward: Practical use and effects on patient outcomes. *PLoS One* 2019;14:e0213402.

12. Weenk M, Koeneman M, van de Belt TH*, et al.* Wireless and continuous monitoring of vital signs in patients at the general ward. *Resuscitation* 2019;136:47-53.

13. Michard F, Gan TJ, Kehlet H. Digital innovations and emerging technologies for enhanced recovery programmes. *Br J Anaesth* 2017;119:31-39.

14. Beg MS, Gupta A, Stewart T*, et al.* Promise of wearable physical activity monitors in oncology practice. *J Oncol Pract* 2017;13:82-89.

15. Leth S, Hansen J, Nielsen OW*, et al.* Evaluation of commercial self-monitoring devices for clinical purposes: Results from the future patient trial, Phase I. *Sensors (Basel)* 2017;17

16. Gillinov S, Etiwy M, Wang R*, et al.* Variable accuracy of wearable heart rate monitors during aerobic exercise. *Med Sci Sports Exerc* 2017;49:1697-703.

17. van Lier HG, Pieterse ME, Garde A*, et al.* A standardized validity assessment protocol for physiological signals from wearable technology: Methodological underpinnings and an application to the E4 biosensor. *Behav Res Methods* 2020;52:607-629.

18. Wang R, Jia W, Mao Z*, et al.* Cuff-free blood pressure estimation using pulse transit time and heart rate. 2014 12th International Conference on Signal Processing (ICSP), 2014:115-18.

19. Gholamhosseini H, Meintjes A, Baig M*, et al.* Smartphone-based continuous blood pressure measurement using pulse transit time. *Stud Health Technol Inform* 2016;224:84-9.

20. Zhang Q, Zhou D, Zeng X. Highly wearable cuff-less blood pressure and heart rate monitoring with single-arm electrocardiogram and photoplethysmogram signals. *Biomed Eng Online* 2017;16:23.

21. Li G, Yu Y, Zhang C*, et al.* An efficient optimization method to improve the measuring accuracy of oxygen saturation by using triangular wave optical signal. *Rev Sci Instrum* 2017;88:093103.

22. Association for the Advancement of Medical Instrumentation. (2002). Cardiac monitors hrm, and alarms. American National Standard (ANSI/AAMI EC13: 2002) Arlington, VA, 1-87.

23. Smolle KH, Schmid M, Prettenthaler H*, et al.* The accuracy of the CNAP® device compared with invasive radial artery measurements for providing continuous noninvasive arterial blood pressure readings at a medical intensive care unit: A method-comparison study. *Anesth Analg* 2015;121:1508-16.

24. Breteler MJMM, Huizinga E, van Loon K*, et al.* Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in the Netherlands: a clinical validation study. *BMJ Open* 2018;8:e020162.

25. Lu MJ, Zhong WH, Liu YX*, et al.* Sample size for assessing agreement between two methods of measurement by bland-altman method. *Int J Biostat* 2016;12

26. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat* 2007;17:571-82.

27. Clarke WL, Cox D, Gonder-Frederick LA*, et al.* Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 1987;10:622-8.

28. Jakob S, Korhonen I, Ruokonen E*, et al.* Detection of artifacts in monitored trends in intensive care. *Comput Methods Programs Biomed* 2000;63:203-9.

FIGURE 1

Placement of the patch sensor

We would like to thank the person who made this Figure possible.

DATA STATEMENT

Data will be available in the Dryad repository.

AUTHOR CONTRIBUTIONS

MLG, PS, PA, MM, and MF contributed to the conception and design of the research protocol.

SM, SA, and BT provided critical input pertaining to the design of the trial interventions and procedures.

MLG, PS, PA, MM, and MF will make substantial contributions to the interpretation of the data.

PA designed the statistical analysis protocol.

MF wrote the first draft of the protocol and this manuscript.

All authors (MLG, PS, SM, SA, BT, MM, PA, and MF) critically revised and modified the protocol and the article. All authors approved the final version to be published. All authors agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

PATIENT CONSENT

Required

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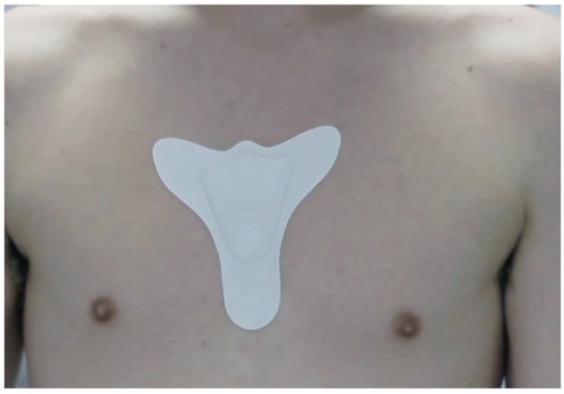

Figure 1

Figure 1

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PATCH VALIDATION: AN OBSERVATIONAL STUDY PROTOCOL FOR THE EVALUATION OF A MULTISIGNAL WEARABLE SENSOR IN PATIENTS DURING ANAESTHESIA AND IN THE POST-ANAESTHESIA CARE UNIT

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Complete List of Authors:	Le Guen, Morgan; Hopital Foch, Department of Anesthesiology Squara, Pierre; Clinique Ambroise Pare, ICU Ma, Sabrina; Hopital Foch, Department of Anesthesiology Adjavon, Shérifa; Hopital Foch, Department of Anesthesiology Trillat, Bernard; Hôpital Foch, Department of Information Systems Merzoug, Messaouda; Clinique Ambroise Pare, Research Unit Aegerter, Philippe; GIRCI-IdF, 75019 Paris, France, Methodology Unit; Paris-Saclay University, UVSQ, INSERM, , U1018 (Center for Epidemiology and Population Health) Fischler, Marc; Hopital Foch, Anesthesia
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PATCH VALIDATION: AN OBSERVATIONAL STUDY PROTOCOL FOR THE EVALUATION OF A MULTISIGNAL WEARABLE SENSOR IN PATIENTS DURING ANAESTHESIA AND IN THE POST-ANAESTHESIA CARE UNIT

Abbreviated title: Validation of a multisignal wearable sensor

Morgan Le Guen,[1] Pierre Squara,[2] Sabrina Ma,[1] Sherifa Adjavon,[1] Bernard Trillat,[3]

Messaouda Merzoug,[2] Philippe Aegerter,[4] Marc Fischler[1]

Author affiliations

[1] Hôpital Foch, Department of Anaesthesiology, 92150 Suresnes, France, and Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

[2] Research Unit, Centre Médico-Chirurgical Ambroise Paré, 92200 Neuilly-sur-Seine, France

[3] Hôpital Foch, Department of Information Systems, 92150 Suresnes, France

[4] Methodology Unit, GIRCI-IdF, 75019 Paris, France, and U1018 (Center for Epidemiology and Population Health), Paris-Saclay University, UVSQ, INSERM, 94807, Villejuif, France

Corresponding Author: Marc Fischler, MD, Department of Anaesthesiology, Hospital Foch, 40 rue Worth, 92150 Suresnes, France. E-mail: m.fischler@orange.fr Phone: 0033 1 46 25 24 42 (Business telephone) – 0033 6 09 68 78 54 (Mobile). Fax: 0033 1 46 25 240 88

Contact information for the trial sponsor: Pierre Squara, Research Unit, Centre Médico-Chirurgical Ambroise Paré, Neuilly-sur-Seine, France. E-mail: pierre.squara@orange.fr.

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ABSTRACT

Introduction: Except for operating rooms, post-anaesthesia care units and intensive care units, where the monitoring of vital signs is continuous, intermittent care is standard practice. However, at a time when only the patients with the most serious conditions are hospitalised and only a fraction of these patients are in intensive care units, this type of monitoring is no longer sufficient. Wireless monitoring has been proposed, but it requires rigorous validation. The aim of this observational study is to compare vital signs obtained from a precordial patch sensor to those obtained with conventional monitoring.

Methods and analysis: This patch validation trial will be an observational, prospective, single-centre open study of 115 anaesthetised adult patients monitored with both a wireless sensor (myAngel VitalSigns™, Devinnova, Montpellier, France) and a standard bedside monitor (Carescape Monitor B850, GE Healthcare, Chicago, Illinois). Both sensors will be used to record peripheral oxygen saturation, respiratory rate, heart rate, body temperature, and blood pressure (systolic and diastolic). The main objective will be to assess the degree of agreement between the two systems during the patients' stay in the post-anaesthesia care unit, both at the raw signal level and at the clinical parameter level. The secondary objectives will be to assess the same performance under anaesthesia, the frequency of missing data or artefacts, the diagnostic performance of the systems, the influence of patients' characteristics on agreement between the two systems, the adverse events and the acceptability of the patch to patients. Bland-Altman plots will be used in the main analysis to detect discrepancies and estimate the limits of agreement.

Ethics and dissemination: Ethics approval was obtained from the Ethical Committee (Toulouse, France) on April 10, 2020. We are not yet recruiting subjects for this study. The results will be submitted for publication in peer-reviewed journals. The trial registration number on ClinicalTrials.gov is NCT04344093.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to validate a new multisignal wearable sensor in patients when they are under anaesthesia and in the post-anaesthesia care unit, which are times when signal artefacts commonly occur.

- The study results will help determine the level of agreement between the parameters collected by a conventional monitor and the patch (in particular, blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature).

- The study results will also estimate the frequency of artefacts and determine the acceptability of this patch to patients during their stay in the post-anaesthesia care unit.

- Validation of this device during anaesthesia and PACU stay could not however be generalized to the postoperative period in the ward where patients are more mobile with an increased risk of artifacts.

INTRODUCTION

Although some surgical patients with severe comorbidities or complications are hospitalised in units with a high level of monitoring, most patients are hospitalised in conventional units where clinical supervision is infrequent, particularly during the night.[1]

Adverse events occur frequently after surgery, as shown by a prospective international 7-day cohort study of outcomes following elective adult inpatient surgery in 44 814 patients in 27 countries. A total of 7 508 patients (16.8%) developed one or more postoperative complications, and 207 patients (0.5%) died.[2] Hospital costs are significantly increased by these complications,[3] which are largely due to the inability to quickly detect significant worsening of a patient's condition.[4]

To improve nurses' ability to assess a patient's clinical situation, the Early Warning Score (EWS) is measured repeatedly. This score initially included five physiological parameters: heart rate, systolic blood pressure, respiratory rate, temperature and consciousness level.[5] Many variants that include additional variables, such as oxygen saturation, urine output, and clinical signs of deterioration (pallor, sweating, looking unwell), have been proposed. NHS England promoted the adoption of the National Early Warning Score 2 (NEWS2) for adult patients by March 2019.[6 7] However, studies have shown contradictory results regarding the added value of the EWS in relation to patient outcomes.[8-10]

Alternatively, clinical evaluation by nurses can be augmented by devices that allow the continuous monitoring of vital signs. Toward this end, Philips General Care Solutions proposed an automated Modified Early Warning Score (MEWS) monitoring system, the Philips IntelliVue Guardian Solution (Guardian),[11] and, concerning wearable vital sign monitoring devices, Weenk *et al*. showed that the ViSi Mobile and the HealthPatch give more frequent alerts than do nurses.[12] Michard *et al*. reviewed numerous innovations, particularly those designed to detect respiratory complications using wearable and wireless sensors.[13] Before new sensors can be used, their accuracy and reliability must be verified.[14 15] Validation is of great importance, since the general public can buy lay-user devices that seem similar but do not yield high-quality results. For example, Gillinov *et al*. compared five optical heart rate monitors during various types of aerobic exercise and showed large differences between the monitors and a reference (an electrocardiograph device).[16] Van Lier *et al*. recently reported at least three major

reasons for inadequate validation (the use of different and sometimes inappropriate statistical methods, the evaluation of different levels for each parameter, and a lack of criteria to determine validity) and recently published a standardized protocol for assessing the validity of physiological signals from wearable technology.[17] Many portable wireless monitoring devices, measuring various numbers of physiological parameters, have been subjected to validation studies.[18 19] We have focused our interest on a new device, the myAngel VitalSigns™ (VS), which is a multimodal medical device including three electrocardiography (ECG) leads and sensors that can measure physiological parameters such as blood pressure, heart rate, respiratory rate, peripheral oxygen saturation (SpO_2), actimetry, posture and body temperature. We aim to evaluate this device, which has never been validated or used previously, during patients' post-anaesthesia care unit (PACU) stays (main objective), when their movements can generate artefacts, and during surgical procedures (one of the secondary objectives), when electrocautery and electronic devices can also create artefacts.

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METHODS AND ANALYSIS

Trial design

This prospective observational study will be conducted in an academic hospital in which all types of surgical procedures except cardiac and orthopaedic procedures are performed. The study has not yet recruited patients. They will be consecutively enrolled and followed up for their entire stay in the operating room and the PACU.

Participant eligibility and consent

Patients will be included if they meet all of the following criteria: (1) over 18 and under 85 years of age, (2) general anaesthesia for extra-thoracic surgery, (3) supine position during surgery, and (4) written informed consent. The exclusion criteria are as follows: (1) pregnant or breastfeeding women, (2) patients with previous severe skin reactions to adhesives, and (3) patients deprived of liberty or under guardianship.

The studied device

The VS medical device, which has not yet obtained CE or FDA approval, comprises a reusable electronic module, which allows physiological data to be acquired, and a disposable skin patch, which secures three contact electrodes (Figure 1; Devinnova, 34080 Montpellier, France). Sensors integrated into the electronic module allow the measurement of the following vital parameters: 3-lead ECG signals, oxygen saturation, respiratory rate, heart rate, body temperature, blood pressure (systolic and diastolic), actimetry (distance travelled, speed, number of steps, and posture), and abrupt changes in position (impacts, falls). The electrodes enable signals to be measured from three ECG leads (DI, aVL, and aVR). The patch sensor also includes a dry zinc/air battery (button cell, 1.4 V, 900 mAh), which powers the electronic module and allows the medical device to function for up to 5 days.

The heart rate measurements are based on the detection of R peaks, enabling RR intervals to be analysed. Blood pressure is determined from the pulse transit time and is calculated by proprietary and artificial intelligence methods.[20-22] Respiratory rate is measured from a pressure sensor that evaluates the variation in chest signal amplitude from a sealed chamber at a constant pressure. Oxygen saturation is measured by an infrared

transceiver that maintains constant and homogeneous contact at the emitted wavelength; the reflection measurements make this method reproducible and reliable.[23] The temperature is measured by infrared spectroscopy, which also has high reproducibility over time. A 6-axis accelerometer is used to evaluate the gravitational effect, i.e., a patient's postural position (lying down, resting on the right or left flank, standing, sitting, immobile, moving) as well as actimetry (number of steps, distance covered, speed) and fall detection. The patch is waterproof, and its size is appropriate for daily use.

A mobile device (smartphone with 3G/4G connection, tablet with internet connection, etc.) with Android (version 4.3 or newer) or iOS (version 10.0 or newer) allows the electronic module to be configured and uses identifying information to associate the patient with the medical device. After this configuration process, all data will be recorded and sent to the mobile device via Bluetooth Low Energy (BLE) V4.0 or higher.

The data acquired by the electronic module are stored in the VS medical device and transmitted to the mobile device, which will encrypt the data and transfer them in real time to a dedicated certified health server. The information stored in the medical device itself is also encrypted and is recorded in a local memory operating system in a first-in, first-out (FIFO) manner. When there is no BLE link between the VS device and the mobile device (due to battery depletion or disruption of device pairing), the VS stores the data in its internal memory and automatically repeats the BLE pairing process (via a thread) with the mobile device until it succeeds. The memory of the VS can store data for up to 4 days. When pairing is operational again, the data acquired in real time are transmitted again and become visible on the mobile device (priority data); the data stored in the memory of the VS (resulting from the link break) are parallelized (via a thread) and sent directly to the buffer zone of the mobile device before being transferred to the certified health server.

Raw data and clinical parameters calculated via the VS will be concealed from caregivers in order not to influence care and will be analysed *a posteriori* from the cloud server. The ability to view the data in real time using the connection between the VS and the mobile device will not be used in this study.

Intervention

Patients meeting the study inclusion criteria *a priori* will be identified on the basis of the surgical programme and the elements collected during anaesthesia consultations. Two physicians (SM and SA), collaborators on the study, will meet these patients either the day before the operation or the same morning. They will present the study to the patients and answer any questions that may arise. The patients will decide whether to participate in this study after a period of reflection that they consider sufficient.

After written informed consent is obtained, the skin patch will be placed on the upper part of the sternum (Figure 1).

All recorded data will include an absolute timestamp, where the mobile device is the reference.

Anaesthesia will be induced following a standard protocol with standard monitoring, including electrocardiography, non-invasive arterial blood pressure, pulse oximetry, capnography, and inspiratory and expiratory sevoflurane concentration measurements, as well as train-of-four monitoring (Aisys anaesthesia machine, Carescape Monitor B850, General Electric Healthcare, Chicago, Illinois, USA). After surgery, all patients will be transferred to the PACU, where the usual automated monitoring (electrocardiography, non-invasive arterial blood pressure, pulse oximetry) will be performed and treatment will be administered.

The study will end when the patient leaves the PACU and returns to the surgical ward.

Data collection

Patient characteristics will be collected upon inclusion in the study and will consist of age, sex, American Society of Anesthesiologists classification, body mass index, underlying diseases, and classification of chest hair. Surgical indication, type of surgical procedure, procedural duration, and eventual complications will be collected at the end of the study from the surgical and anaesthetic records.

All intraoperative monitoring variables (blood pressure, heart rate, pulse oximetry, ventilatory variables, including tidal volume, ventilatory frequency, peak and mean airway pressures, and partial tension of end-tidal carbon dioxide pressure) will be collected using a Centricity Anaesthesia® system at a rate of one value per minute. This system is an anaesthesia information management system that automatically collects and stores data in a repository, which can be subsequently exported as a spreadsheet file (GE Healthcare, Buc, France).

All variables monitored in the PACU (blood pressure, heart rate derived from ECG, pulse oximetry, and respiratory rate measured by thoracic impedance) will also be collected using a Centricity Anaesthesia system at one value per minute, except for arterial pressure, which will be measured at a lower frequency (from one measurement per minute to one every 15 minutes according the clinical state of the patient). The data from the patch sensor will not be communicated to the anaesthesiologists, the nurses, or other health care providers during the study period.

Because the main goal of this study is to investigate how postoperative physiological changes can be monitored with the patch, notes about any relevant findings will be made during the study. For example, if a complication occurs, it will be noted with the corresponding date and time and will be linked with the corresponding measurements.

Finally, when a nurse removes the patch, he/she will assess the status of the skin on the following scale: healthy skin (stage 0), redness limited to the contact area between the device and the skin (stage 1), redness extending beyond the contact surface of the device (stage 2), or the appearance of blisters (stage 3). The patient will be asked to evaluate his or her acceptance of the sensor using a 4-point Likert scale (0 = intolerable, 1 = very unpleasant, 2 = slightly unpleasant, 3 = no problem at all).

Outcome measures

Following the proposal of van Lier,[17] the validity of the wearable device will be assessed at three levels: (1) the raw signal level, based on the similarity of the two complete time series issued from the wearable device and from the reference device; (2) the clinical parameter level, comparing the values of blood pressure, heart rate, oxygen saturation and RR interval, averaged over a given time frame (5 minutes); and (3) the clinical event level, with the detection of relevant physiological changes, such as hypotension or hypopnoea, according to prespecified thresholds. The main objective is to determine the level of agreement between the parameters collected by the conventional monitor and the patch sensor (blood pressure, heart rate, respiratory rate, and oxygen saturation) during patients' stay in the PACU.

The secondary objectives are 1) to determine the level of agreement of the measured parameters during anaesthesia; 2) to determine the frequency of artefacts and blank/null outputs from the wearable device and,

more globally, the signal-level validity; 3) to estimate the diagnostic performance of the patch sensor at the event level, 4) to evaluate the influence of patient characteristics (gender, age, chest hair, and body mass index) on the agreement between the two systems), 5) to identify any adverse events, and 6) to determine the acceptability of this patch to patients during their stay in the PACU.

Statistical analysis

Number of patients to be included

The aim of this study is to test the equivalence of two devices in recording the same data for the same patients. There is no standard method for the analysis of discrete time series (raw signal level). Therefore, an approach based on the quality of physiological data recorded (clinical parameter level) was used to calculate the required number of patients.

For heart rate equipment, the recommendations for the limits of acceptable error (boundaries of the Bland-Altman plot) are a difference of ± 5 beats per minute (bpm) or ± 10%, whichever is greater, between the device of interest and a reference device, as proposed by the Association for Advancement of Medical Instrumentation in 2002.[24] On that basis, we adopted these relative limits (± 10%) for all parameters. We extracted possible values for the distribution of differences between a patch and a reference sensor from the papers of Smolle,[25] Breteler[26] and van Lier.[17] Two methods are considered to be in agreement when a predefined maximum allowed difference (Δ) is larger than the higher observed limit of agreement (LoA) and -Δ is smaller than the lower LoA. The 95% confidence interval (CI) of the LoA must be taken into account for proper interpretation. Thus, in order to be 95% certain that the methods do not disagree, Δ must be larger than the upper 95% CI bound of the higher LoA and -Δ must be smaller than the lower 95% CI bound of the lower LoA. We then followed the new method proposed by Lu *et al.* that takes power into account.[27] Thus, assuming a standard deviation of difference in heart rate of 4 bpm, a limit of acceptable error of 10 bpm (i.e., 2.5 times the standard deviation), a two-sided alpha of 5% and a power level of 90%, a sample size of 136 pairs of measures is required. If two measures (m=2) of the same parameter are sampled in the same patient by two devices instead of one, the inclusion of n patients would yield 2n pairs of measures; however, taking into account the intra-patient correlation r, which is usually estimated to be 0.5, the design effect (DE) is 1+ (m-1)r = 1.5. Thus, the non-independence of observations within

the same patient requires 1.5 * 2 * n paired measures to obtain the same amount of information as would be given by one pair of measures for each of 2*n independent patients. Therefore, the need for 136 independent pairs indicates that 136/1.5 = 90 patients need to be measured on two occasions by the two devices being assessed. This sample size is overestimated, since more than two measurement pairs could be obtained for each patient. However, it will also allow us i) to analyse agreement at the clinical event level, those events being much less frequent than the sampling points, and ii) to perform an agreement analysis according to prespecified subgroups, defined by gender, age, body mass index, and quantity of chest hair.

Taking into account that approximately 20% of the data may be unusable, it is anticipated that 115 patients need to be included in the study to ensure that the data of 90 patients (with two paired measurements, each in the postoperative period) can be analysed.

Detection of artefacts

A value will be automatically considered an artefact before data analysis if it is outside one of the "normal" ranges defined in previous studies:[12 28-30] 1) a value that is > 50% different from the previous value, unless it is followed by a value equal to ± 25%; or 2) a value that is out of the physiologically plausible range (heart rate < 5 or > 250 bpm, systolic artery pressure < 20 mm Hg or > 300 mm Hg or less than diastolic pressure plus 5 mm Hg, diastolic artery pressure < 5 mm Hg or > 225 mm Hg, SpO_2 change of ≥ 8% between two consecutive measurements, respiratory rate < 3 or > 60 breaths per minute, skin temperature change of ≥ 1° between two consecutive measurements). Furthermore, two clinicians will independently review all data in graphical form (one graph per variable per patient) before and after the artefacts are automatically identified. A third clinician will also review the data when there is discordance between the first two.

The selected rules to define artefacts may be updated according to experience. The adjusted rules will be recorded in a register, and all recordings will be reviewed in light of these new rules.

Statistical analyses of reliability and agreement

Descriptive summaries will be provided for each parameter and for each device. For continuous variables, the mean, median and their 95% confidence limits, obtained using bootstrapping, will be provided. For discrete variables, counts, percentages and confidence limits, obtained using bootstrapping, will be provided. The relative frequency of data gaps and artefacts for each parameter will be given as a percentage of the total number

of measurement points and of observations, respectively, with the corresponding 95% CIs. The delay (hours) to the first occurrence of data loss or loss of device functionality will be described and analysed with Kaplan-Meier survival curves.

At the signal level (i.e., for any physiological variable), cross-correlation will be used to compare the wearable device to a reference along the time series for each participant. If the cross-correlation coefficient is greater than 0.8 for all participants, the level of agreement will be deemed acceptable, and the assessment will be completed by calculating the differences. Complementarily, we will search for any systematic difference in mean or variance to correct the data from the wearable device.

At the parameter level, Bland-Altman analysis for repeated measurements, which accounts for multiple observations per individual, will be performed to create mean-difference plots and compare the accuracy or bias (mean difference), precision (standard deviation of difference), and the LoAs that are expected to contain 95% of paired differences between the measurements taken by the two methods (and their CIs), with those reported in the literature. A generalized linear mixed model (GLMM) will be used to calculate the components of variance, notably the within-subject variation, to correct the variance of differences in this context of repeated measures.[31 32] If the 95% CIs for the 95% LoAs are within the predefined agreement limits that are clinically acceptable, the two methods will be considered to have sufficient agreement to fulfil the agreement requirements.

In addition, a Clarke error grid analysis, with standard predetermined grids for heart rate, respiratory rate, artery pressure, SpO_2, and temperature, will be conducted to identify the consequences of clinical decisions.[33]

For adverse events, such as bradycardia, the sensitivity and specificity of the wearable device compared with the reference sensor will be calculated with 95% CIs.

Data from the postoperative period and the intraoperative period will be analysed separately.

A two-tailed p value < 0.05 will be considered statistically significant, without any adjustment for multiplicity.

All statistical analyses will be performed using R software (version 3.2.4).

Missing values

Missing data will not be imputed.

Data registration

Data will be entered into the electronic case report form (eCRF) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF, the trial database will be established. The data collection process will be monitored by trained research coordinators.

Patient withdrawal

Any participant who wishes to terminate his/her participation in the study will be allowed to withdraw from the trial at any time without the need for further explanation. Participants who withdraw from the study will be followed up according to routine clinical practice.

Safety

Every serious adverse event (SAE) related to the studied procedure, regardless of whether it was expected, will be reported by the investigator to the sponsor within 24 hours on an SAE form that will list the date of occurrence, the criterion used to define severity, the intensity, the relationship with the study, and the outcome. The period in which SAEs should be reported will last from the day written informed consent is obtained to the end of the follow-up period. Whenever an SAE persists at the end of the study, the investigator will follow the patient until the event is considered resolved. The management of SAEs will follow regulations and good clinical practices.

Data handling and retention

The data will be handled according to French laws under the responsibility of the Research Unit, Centre Médico-Chirurgical Ambroise Paré (Neuilly-sur-Seine, France). All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondence) will be archived at the trial sites for 15 years. The cleaned and frozen trial database files will be anonymised and stored for 15 years.

Patient and public involvement

Patients and the public will not be involved in any phase of this study.

Limitations

A limitation of this study is that we will compare only minute-by-minute data. More sophisticated technologies that can be used to detect artefacts when monitoring trends in intensive care are as follows: (1) the Rosner statistic; (2) slope detection with rules; and (3) comparisons with a running median (median detection).[34]

Some categories of patients will not be included in the study: pregnant or breastfeeding women will be excluded because of French regulatory constraints, and patients older than 85 years will be excluded because they frequently present tremors, a well-known cause of artefacts.

Validation of the device in this study, where patients were monitored during their anaesthesia and PACU stays, does not allow us to generalize the possible favourable results to other situations. For example, such results could not be generalized to the postoperative period in the ward, where the risk of artefacts is elevated due to the patients' increased mobility. Similarly, it will be necessary to specifically study very elderly patients, given the frequency of tremors in that population, as tremors can be a source of artefacts.

ETHICS AND DISSEMINATION

Ethics

Ethics approval for this patch validation trial was obtained from the Ethical Committee (Toulouse, France) on April 10, 2020. Written informed consent will be required from patients prior to their participation in the study. The patch validation trial is registered at ClinicalTrials.gov with the trial identification number NCT04344093. We are not yet recruiting subjects for this study.

Dissemination

The STROBE Statement (checklist of items that should be included in reports of cohort studies) will be followed.

Publication plan

Scientific presentations and reports derived from the study will be written under the responsibility of the coordinating investigator of the study with the approval of the principal investigators and the methodologist. The co-authors of the report and publications will be the investigators and clinicians involved, in proportion to their contributions to the study, as well as the biostatistician and associated researchers. The international recommendations for authorship will be followed.

REFERENCES

1. Churpek MM, Edelson DP, Lee JY, *et al.* Association Between Survival and Time of Day for Rapid Response Team Calls in a National Registry. *Crit Care Med* 2017;45:1677-82.
2. International Surgical Outcomes Study g. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016;117:601-09.
3. Michard F, Mountford WK, Krukas MR, *et al.* Potential return on investment for implementation of perioperative goal-directed fluid therapy in major surgery: a nationwide database study. *Perioper Med (Lond)* 2015;4:11.
4. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med* 2009;361:1368-75.
5. Morgan RJM, Williams F, Wright M. An early warning scoring system for detecting developing critical illness. *Clin Intensive Care* 1997;8:100.
6. . Available from: https://improvement.nhs.uk/documents/3657/Resources_to_support_the_adoption_of_NEWSFINAL.PDF.
7. https://www.england.nhs.uk/ourwork/clinical-policy/sepsis/nationalearlywarningscore/news-frequently-asked-questions/#4-why-has-a-news2-been-launched.
8. McGaughey J, Alderdice F, Fowler R, *et al.* Outreach and Early Warning Systems (EWS) for the prevention of intensive care admission and death of critically ill adult patients on general hospital wards. *Cochrane Database Syst Rev* 2007:CD005529.
9. Alam N, Hobbelink EL, van Tienhoven AJ, *et al.* The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. *Resuscitation* 2014;85:587-94.
10. Shamout F, Zhu T, Clifton L, *et al.* Early warning score adjusted for age to predict the composite outcome of mortality, cardiac arrest or unplanned intensive care unit admission using observational vital-sign data: a multicentre development and validation. *BMJ Open* 2019;9:e033301.
11. Mestrom E, De Bie A, Steeg MV, *et al.* Implementation of an automated early warning scoring system in a surgical ward: Practical use and effects on patient outcomes. *PLoS One* 2019;14:e0213402.

12. Weenk M, Koeneman M, van de Belt TH, *et al.* Wireless and continuous monitoring of vital signs in patients at the general ward. *Resuscitation* 2019;136:47-53.

13. Michard F, Gan TJ, Kehlet H. Digital innovations and emerging technologies for enhanced recovery programmes. *Br J Anaesth* 2017;119:31-39.

14. Beg MS, Gupta A, Stewart T, *et al.* Promise of Wearable Physical Activity Monitors in Oncology Practice. *J Oncol Pract* 2017;13:82-89.

15. Leth S, Hansen J, Nielsen OW, *et al.* Evaluation of Commercial Self-Monitoring Devices for Clinical Purposes: Results from the Future Patient Trial, Phase I. *Sensors (Basel)* 2017;17

16. Gillinov S, Etiwy M, Wang R, *et al.* Variable Accuracy of Wearable Heart Rate Monitors during Aerobic Exercise. *Med Sci Sports Exerc* 2017;49:1697-703.

17. van Lier HG, Pieterse ME, Garde A, *et al.* A standardized validity assessment protocol for physiological signals from wearable technology: Methodological underpinnings and an application to the E4 biosensor. *Behav Res Methods* 2020;52:607-29.

18. Breteler MJM, KleinJan EJ, Dohmen DAJ, *et al.* Vital Signs Monitoring with Wearable Sensors in High-risk Surgical Patients: A Clinical Validation Study. *Anesthesiology* 2020;132:424-39.

19. Leenen JPL, Leerentveld C, van Dijk JD, *et al.* Current Evidence for Continuous Vital Signs Monitoring by Wearable Wireless Devices in Hospitalized Adults: Systematic Review. *J Med Internet Res* 2020;22:e18636.

20. Wang R, Jia W, Mao Z, *et al.* Cuff-free blood pressure estimation using pulse transit time and heart rate. 2014 12th International Conference on Signal Processing (ICSP), 2014:115-18.

21. Gholamhosseini H, Meintjes A, Baig M, *et al.* Smartphone-based Continuous Blood Pressure Measurement Using Pulse Transit Time. *Stud Health Technol Inform* 2016;224:84-9.

22. Zhang Q, Zhou D, Zeng X. Highly wearable cuff-less blood pressure and heart rate monitoring with single-arm electrocardiogram and photoplethysmogram signals. *Biomed Eng Online* 2017;16:23.

23. Li G, Yu Y, Zhang C, *et al.* An efficient optimization method to improve the measuring accuracy of oxygen saturation by using triangular wave optical signal. *Rev Sci Instrum* 2017;88:093103.

24. Association for the Advancement of Medical Instrumentation. (2002). Cardiac monitors hrm, and alarms. American National Standard (ANSI/AAMI EC13: 2002) Arlington, VA, 1-87.

25. Smolle KH, Schmid M, Prettenthaler H*, et al.* The Accuracy of the CNAP(R) Device Compared with Invasive Radial Artery Measurements for Providing Continuous Noninvasive Arterial Blood Pressure Readings at a Medical Intensive Care Unit: A Method-Comparison Study. *Anesth Analg* 2015;121:1508-16.

26. Breteler MJMM, Huizinga E, van Loon K*, et al.* Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in the Netherlands: a clinical validation study. *BMJ Open* 2018;8:e020162.

27. Lu MJ, Zhong WH, Liu YX*, et al.* Sample Size for Assessing Agreement between Two Methods of Measurement by Bland-Altman Method. *Int J Biostat* 2016;12

28. Morillo DS, Gross N. Probabilistic neural network approach for the detection of SAHS from overnight pulse oximetry. *Med Biol Eng Comput* 2013;51:305-15.

29. Cunningham S, Symon AG, McIntosh N. The practical management of artifact in computerised physiological data. *Int J Clin Monit Comput* 1994;11:211-6.

30. Kool NP, van Waes JA, Bijker JB*, et al.* Artifacts in research data obtained from an anesthesia information and management system. *Can J Anaesth* 2012;59:833-41.

31. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat* 2007;17:571-82.

32. Myles PS, Cui J. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth* 2007;99:309-11.

33. Clarke WL, Cox D, Gonder-Frederick LA*, et al.* Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 1987;10:622-8.

34. Jakob S, Korhonen I, Ruokonen E*, et al.* Detection of artifacts in monitored trends in intensive care. *Comput Methods Programs Biomed* 2000;63:203-9.

FIGURE 1

Placement of the patch sensor

We would like to thank the person who made this Figure possible.

DATA STATEMENT

Data will be available in the Dryad repository.

AUTHOR CONTRIBUTIONS

MLG, PS, PA, MM, and MF contributed to the conception and design of the research protocol.

SM, SA, and BT provided critical input pertaining to the design of the trial interventions and procedures.

MLG, PS, PA, MM, and MF will make substantial contributions to the interpretation of the data.

PA designed the statistical analysis protocol.

MF wrote the first draft of the protocol and this manuscript.

All authors (MLG, PS, SM, SA, BT, MM, PA, and MF) critically revised and modified the protocol and the article. All authors approved the final version to be published. All authors have agreed to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

PATIENT CONSENT

Required

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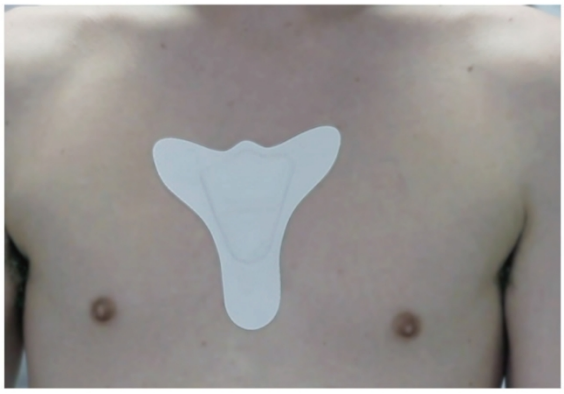

Figure 1

Figure 1

160x99mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Note that several items are noted Not Applicable (NA) since the manuscript is the protocol of an upcoming study

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 (no results)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	11 (artifacts)
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			NA (publication of a protocol)
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	--
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	--

		(b) Indicate number of participants with missing data for each variable of interest	--
		(c) Summarise follow-up time (eg, average and total amount)	--
Outcome data	15*	Report numbers of outcome events or summary measures over time	--
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	--
		(*b*) Report category boundaries when continuous variables were categorized	--
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.