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Remote Monitoring of Vital and Activity Parameters in Chronic Transfusion-Dependent Patients: A Feasibility Pilot Using Wearable Biosensors

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Keywords
Red blood cell transfusion · Remote monitoring · Physiological parameters · Cognition

Abstracts
Introduction: Little is known if, and to what extent, outpatient red blood cell (RBC) transfusions benefit chronic transfusion-dependent patients. Costs, labour, and potential side effects of RBC transfusions cause a restrictive transfusion strategy to be the standard of care. However, effects on the actual performance and quality of life of patients who require RBCs on a regular basis are hardly studied. The aim of this study was to assess if new technologies and techniques like wearable biosensor devices and web-based testing can be used to measure physiological changes, functional activity, and hence eventually better assess quality of life in a cohort of transfusion-dependent patients. ***Methods:*** We monitored 5 patients who regularly receive transfusions during one transfusion cycle with the accelerateIQ biosensor platform, the Withings Steel HR, and web-based cognitive and quality of life testing. ***Results:*** Data collection by the deployed devices was shown to be feasible; the AccelerateIQ platform rendered data of which 97.8% was of high quality and usable; of the data the Withings Steel HR rendered, 98.9% was of high quality and usable. Furthermore, heart rate decreased and cognition improved significantly following RBC transfusions. Activity and quality of life measures did not show transfusion-induced changes. ***Conclusion:*** In a 5-patient cohort of transfusion-dependent patients, we found that the accelerateIQ, Withings Steel HR, and CANTAB platforms enable acquisition of high-quality data. The collected data suggest that RBC transfusions significantly and reversibly decrease heart rate and increase sustained attention in this cohort. This feasibility study justifies larger validation trials to confirm that these wearables can indeed help to determine personalized RBC transfusion strategies and thus optimization of each patient's quality of life.

Introduction

Only few completed trials in the outpatient setting for transfusion-dependent patients have been conducted [1, 2], and there is little data in general about the value of

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Table 1. Patient baseline characteristics

	R001	R002	R003	R004	R005
Age, years	70–79	70–79	70–79	20–29	70–79
Haematological disorder	MDS	MDS	MDS	β-Thalassemia	MDS
Uses a β-blocker	No	Yes	No	No	No
RBCs per transfusion episode	2	2	1	1	2
Pre-transfusion haemoglobin at V1	9.0 g/dL	8.7 g/dL	8.7 g/dL	8.7 g/dL	10.0 g/dL
V4	7.7 g/dL	9.2 g/dL	8.7 g/dL	8.4 g/dL	10.0 g/dL
Sex	Female	Male	Male	Female	Male
Transfusion interval	3 weeks	2 weeks	2 weeks	5 weeks	3 weeks

MDS, myelodysplastic syndrome; RBC, red blood cell.

outpatient transfusions [3–7]. Adverse events of red blood cell (RBC) transfusions, like transfusion reactions [8–10], iron overload [11–13], and poor clinical outcomes in studies with liberal transfusion thresholds in patients with acute anaemia [14–17] are reasons for a default restrictive transfusion strategy. Without objective parameters to measure the benefits of RBC transfusions, a restrictive transfusion strategy might not be the optimal choice for deeply anaemic patients that require RBC transfusions on a regular basis.

The current standard of transfusion care in these patients typically involves 1–3 units administered every 2–4 weeks and is based on a combination of haemoglobin concentrations and a subjective interpretation of clinical symptoms of anaemia. Validated measurements of quality of life and performance measures, however, might be more clinically relevant. More elaborated upon, thresholds for timing of transfusion could be the patient's vital signs and functional activity. Although such data can nowadays be obtained by wearable telemetric tools, systematic assessment of such tools and their data have not yet been performed. Moreover, this is a prerequisite for eventual randomized trials examining the impact of RBC transfusion on such outcomes in transfusion-dependent patients. Because haemoglobin concentration and VO_2max are correlated [18], the increased oxygen transport capacity following RBC transfusion may result in a reduced cardiac output, with, hence, a reduced heart rate. This may subsequentially lead to an increase in quality of life (QoL) and activity parameters. Furthermore, since correlations between altitude and cognition, through altitude-induced hypoxia, have been established [19–21], patients with chronic anaemia might endure similar hypoxia-induced cognitive changes.

The aim of this study was therefore to understand if new technologies and techniques like wearable biosensor devices and web-based testing can be used to measure physiological changes and functional activity in a pilot cohort of transfusion-dependent patients. To evaluate this, we hypothesized that patients' heart rates should decrease significantly after a single RBC transfusion, while returning to baseline before the subsequent transfusion. Furthermore, we tested whether the haemoglobin changes inherent to intermittent RBC transfusion also measurably modulate cognition, activity, and patient-reported QoL. Eventually, objective outcomes like a decrease in activity and vital sign changes due to chronic anaemia and the reverse after RBC transfusion may help inform guidelines on who, when, and how to transfuse as restrictively as possible without compromising QoL.

Methods

Study Design

The present study was a single-centre, observational, within-subject design, feasibility pilot study performed by the Haga Teaching Hospital. The study aimed to assess the feasibility of extracting and analysing data in a larger cohort and explore RBC transfusion-induced changes in vital sign, activity, cognitive, and QoL parameters. The study population was comprised of 5 patients with chronic dependence on RBC transfusion (at least one transfusion every 8 weeks) due to a haematological disorder. Patients with severe pulmonary comorbidities, arrhythmias, or other significant conductivity disorders, or with known skin conditions that might compromise the device's quality of data were excluded. Patients were their own controls as data before and after RBC transfusion were compared. Recruitment was between November 2019 and April 2020 by patients' own physician. The follow-up lasted until May 2020. Most of the data were collected remotely with the patients being at home.

Intervention

Patients received RBC transfusions according to their own usual transfusion regimen. This varied between 1 and 2 units every 2–5 weeks (Table 1). Conforming to the Dutch blood transfusion

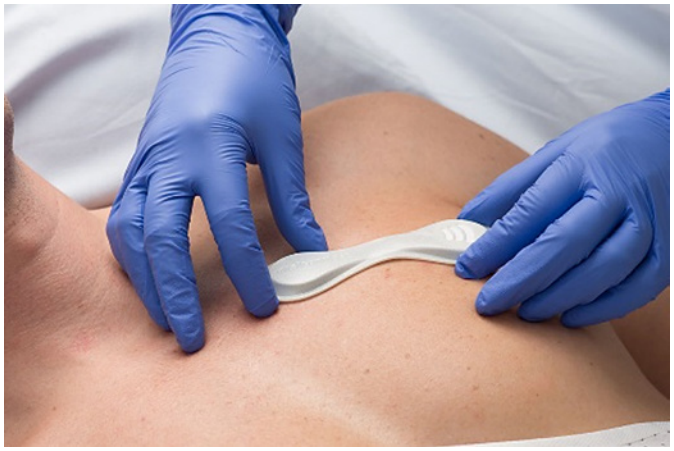

Fig. 1. The VitalPatch®, a single-lead, wet-electrode device that collects electrocardiogram and triaxial accelerometery data, used for the AccelerateIQ™ platform.

Fig. 2. The Withing Steel HR watch. This device uses photoplethysmography to semi-continuously monitor heart rate and has a triaxial accelerometer for activity data.

guidelines, transfusion-dependent myelodysplastic syndrome and thalassemia patients receive Rh and Kell compatible RBCs to prevent the formation of allo-antibodies.

Data Collection and Outcome Measures

Patients were monitored 7 days before the target RBC transfusion and up to the subsequent transfusion. Two wearable device platforms were used simultaneously to evaluate the usability of collected data: 1. The physIQ accelerateIQ™ platform and 2. The Withings Steel HR watch. AccelerateIQ™ leverages the VitalPatch® (Fig. 1), a single-lead, wet-electrode device that collects electrocardiogram and triaxial accelerometery data to extract various physiological metrics such as heart rate, RR-interval, heart rate variability, respiratory rate, and activity measures (including but not limited to steps, bouts, gait). The Withing Steel HR watch (Fig. 2) uses photoplethysmography to semi-continuously monitor heart rate and a triaxial accelerometer for activity measures; every 10 min, the HR measures the heart rate for ± 30 s and summarizes this into a mean heart rate. The heart rate as measured by the Withings steel HR is divided into a sleeping and awake heart rate by default. The wearables' data are sent via Bluetooth to a mobile phone, which uploads the data over mobile data networks to either the Withings data cloud or the physIQ accelerateIQ™ cloud platform.

The primary outcome of this pilot is the feasibility of capturing physiological data with wearable biosensors. Feasibility was established if the deployed devices captured high quality and usable physiological data >80% of the time in at least 4/5 of the included patients. Secondary outcomes are difference in heart rate, activity, cognition, and QoL before and after RBC transfusion. To assess the effect of RBC transfusion on cognitive and QoL parameters, the Rapid Visual Processing (RVP) task (CANTAB, Cambridge, online suppl. material 4; see www.karger.com/doi/10.1159/000526438 for all online suppl. material) and QoL questionnaires (QUALMS and PROMIS) were used. We selected the robust, validated RVP task to assess the cognitive domain of sustained attention as this has been shown to be impaired at high altitude [20]. The QUALMS (Quality of Life in Myelodysplasia Scale) was created and validated to measure quality of life in myelodysplastic syndrome patients specifically [22].

PhysIQ operates within the US standards for the privacy of health information and regulations for electronic records and signatures, pursuant to the Health Insurance Portability and Accountability Act of 1996 and the Code of Federal Regulations, respectively. Handling of the Withings data is in line with the European General Data Protection Regulation.

Statistical Analysis

Continuous data were summarized as medians per day with interquartile range (IQR) and categorial data as frequencies and percentages. A linear mixed model with random intercept analysis was performed to assess for inference and correct for predefined confounders: age, sex, activity (steps/24 hr), use of β-blocker, and cumulative number of RBCs received per transfusion episode. Data were reviewed for usability in further trials. We used linear interpolation for missing data.

Four "visits" were defined for the analysis: with 2 days before RBC transfusion as visit 1 (V1); 3 days after RBC transfusion as V2; 1 week after RBC transfusion as V3; and 2 days before the subsequent RBC transfusion as V4. To avoid bias due to the natural variability in heart rate and steps, for analysis we used the heart rates and activity of the 3 days around the defined day of visit.

Results

Baseline Data

Five chronic transfusion-dependent patients were included between December 2019 and April 2020 and completed follow-up. Four patients had myelodysplastic syndrome and one had β-thalassemia. RBC transfusion poli-

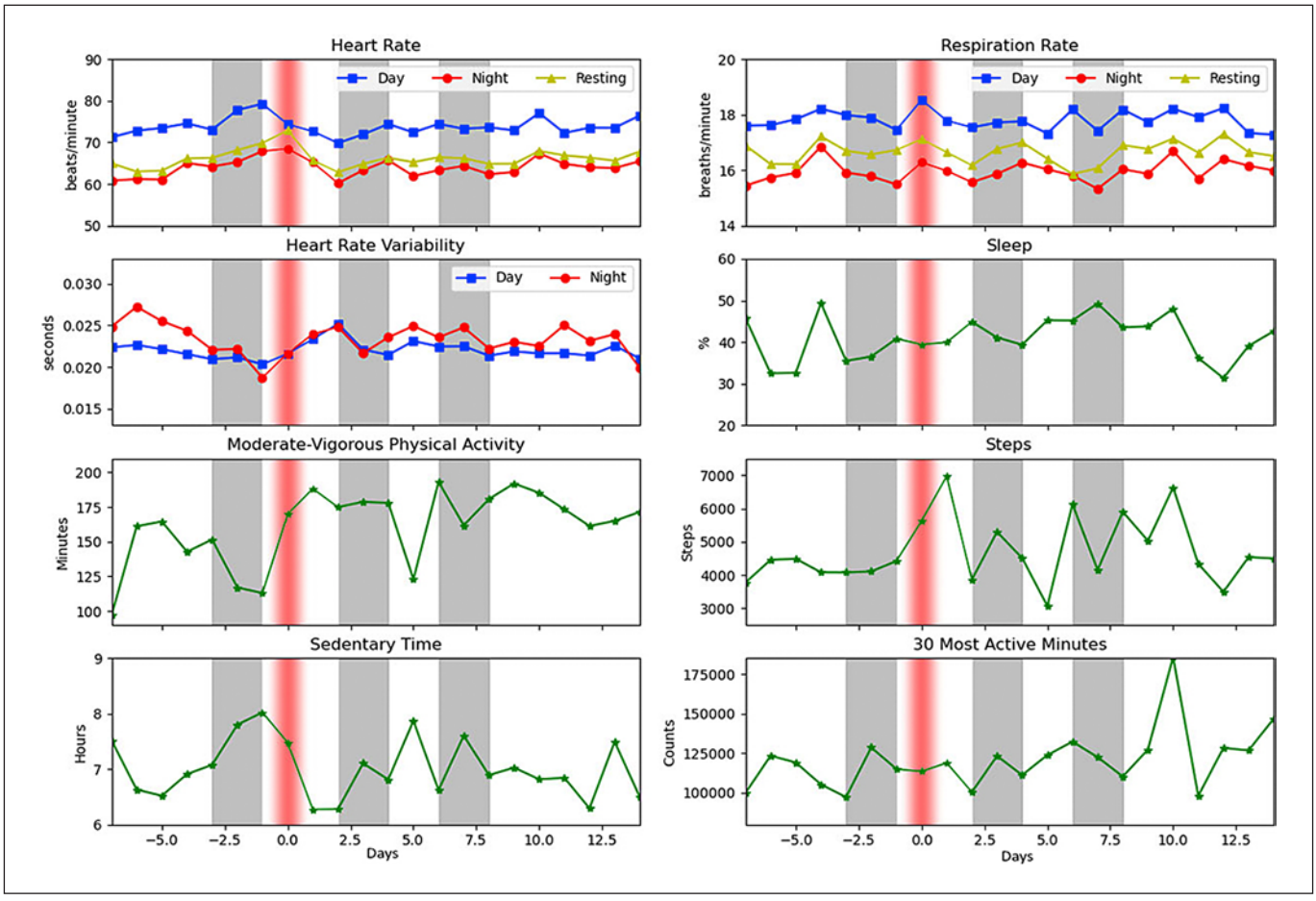

Fig. 3. Population changes of various aggregated values from accelerateIQ before and after transfusion. The graph shows data only until day 14 because 2/5 patients received another transfusion at day 15. Data summarized as V1, V2, and V3 are shown as grey areas; V4 is defined as the last 3 days before the next transfusion, which varies among patients, and can thus not be shown in this graph. Transfusion day results, indicated with the red zone, should be interpreted differently because of their clear aberrance with normal at home days (outcomes per individual in supplementary material 1).

cies varied between one and two units every two to 5 weeks (Table 1). One patient did not complete the PROMIS-questionnaires.

VitalPatch Findings

In a total of almost 132 captured subject days, 13,627,202 data points were collected. Each datapoint represents one RR-interval, and then beat-to-beat heart rate is calculated and windowed into 1-min averages. In total, there were 3,148 h of data, of which 97.8% was high quality, usable data as determined by applying an AI-based signal quality index (SQI) algorithm to the ECG waveform data. The low-quality data were sporadic and not confined to any single subject or time of day. Activity-based parameters were collected in a similar manner.

The heart rate across all subjects noticeably decreased following transfusions with, again, a steady increase in the days leading up to the next transfusion (Fig. 3; online suppl. Material 1). The mean difference in daily heart rate at V1 and V2 was −4.2 ± 0.6 bpm. For the heart rate at night, this was −2.1 ± 1.3 bpm. From V2 to V3, the daily heart rate increased by 2.3 ± 0.6 bpm. Activity levels, as measured by steps, lacked a consistent trend across the study period (Table 2).

Withings Steel HR Findings

In a total of 137 captured subject days, 33,181 data points were collected. Each datapoint is generated by calculating a heart rate for at least 30 s, once every 10 min. One day (0.7%) and two nights (1.5%) of heart rate

Table 2. Outcomes per 3 days from accelerateIQ, Withings, CANTAB, and HR-QoL questionnaires

Feature	Visit 1		Visit 2		Visit 3		Visit 4	
	median	IQR	median	IQR	median	IQR	median	IQR
AccelerateIQ								
Day heart rate, bpm	77.5	9.9	74.9*	8.2	77.0	10.4	73.6	15.2
Night heart rate, bpm	64.0	10.5	61.2	9.4	62.1	9.5	67.5	8.0
Resting heart rate, bpm	67.9	9.3	66.7*#	9.9	65.5#	7.8	67.2	7.2
Day respiratory rate, rpm	17.7	3.0	16.9	2.7	17.1	4.2	18.5	2.8
Night respiratory rate, rpm	16.2	3.2	15.1	3.5	14.5	3.9	19.1	2.7
Resting respiratory rate, rpm	16.8	2.1	15.8	2.8	15.4	3.7	18.9	1.8
Day heart rate variability, sec	0.019	0.005	0.019	0.008	0.021	0.005	0.016	0.008
Night heart rate variability, sec	0.018	0.010	0.021	0.009	0.019	0.018	0.011	0.009
Sleep efficiency, %	33.8	11.3	37.5	32.9	45.8	39.0	31.1	12.4
MVPA, minutes	116.0	69.0	152.5	137.8	165.0*	96.0	182.0	130.0
Daily steps, step count	4,513	2,144	4,751	1,561	4,852	1,851	4,664	920
Sedentary hours, hr	7.3	1.9	6.8	2.3	7.6	1.7	7.7	3.5
30 Most active minutes, counts	67,007	24,603	76,923#	21,466	60,543	66,597	59,106	7,440
Withings								
Day heart rate, bpm	77.0	9.0	73.0*#	6.0	76.7	11.4	76.3	9.0
Night heart rate, bpm	66.0	10.5	63.5*#	11.0	66.0	10.5	68.0	7.0
Daily Steps (count)	1,764	2,239	1,626	1,329	2,033	2,306	1,368	1,487
CANTAB								
RVPA (score)	8,660	74	8,948*	191	9,057*#	411	8,682	267
QUALMS								
QUALMS (score)	61.4	16.1	66.7	12.9	69.7	4.5	68.2	12.1
PROMIS								
Physical (score)	40.8	19	41.8	17.4	42.4	148	45.9	12.8

*$p < 0.05$ compared to V1. #$p < 0.05$ compared to V4, leveraging mixed models; MVPA, moderate to vigorous physical activity; sleep efficiency, percentage of time spent asleep when in bed; bpm, beats per minute; rpm, respiratory rate per minute; 30 most active minutes (counts), a metric for motion: sum of 30 most active minutes per day.

data were insufficient to be included in the analysis. Data were assumed to be sufficient when the heart rate was captured more than 80% of the time. Activity data were collected continuously and summarized as steps per day.

A decrease in heart rate was observed 3 days after RBC transfusion (V2) compared to V1 (Table 2; Fig. 4). The mean difference in daily heart rates between V1 and V2 was −4.2 ± 0.5 bpm (p = 0.016). At night, the mean difference was −3.4 ± 0.7 bpm (p = 0.023). At V3, the daily heart rate was still lower than before transfusion but had increased compared to V2 (V3-V1: −1.1 ± 1.0 bpm, p = 0.007). The heart rate at V4 approximated that of V1.

Comparing the patient's activity as the number of steps at the visits, an increase in activity is found after a week (V1: 1,860 ± 536 steps; V3: 3,004 ± 981). This is not significant, though (p = 0.07) and is visually not supported by Figure 4.

CANTAB Cognitive Evaluation

There was no missingness in our CANTAB data. All patients completed their cognitive tests on the appointed days of visit.

As depicted in Figure 4, patients appear to benefit cognitively from the transfusion. Compared to V1, the mean RVPA at V2 and V3 increased significantly (p = 0.005 and 0.003, resp., Table 2.)

QoL Questionnaires

QoL questionnaires were completed intermittently according to a weekly schedule apart from the visits. We were able to pair a completed QUALMS with each visit for each patient. One patient, unfortunately, did not complete the PROMIS-questionnaires and was omitted from the analysis. There were no significant changes over the study period for any of the derived features from the PROMIS or the QUALMS questionnaires, suggesting that subjective responses do not clearly reflect the detect-

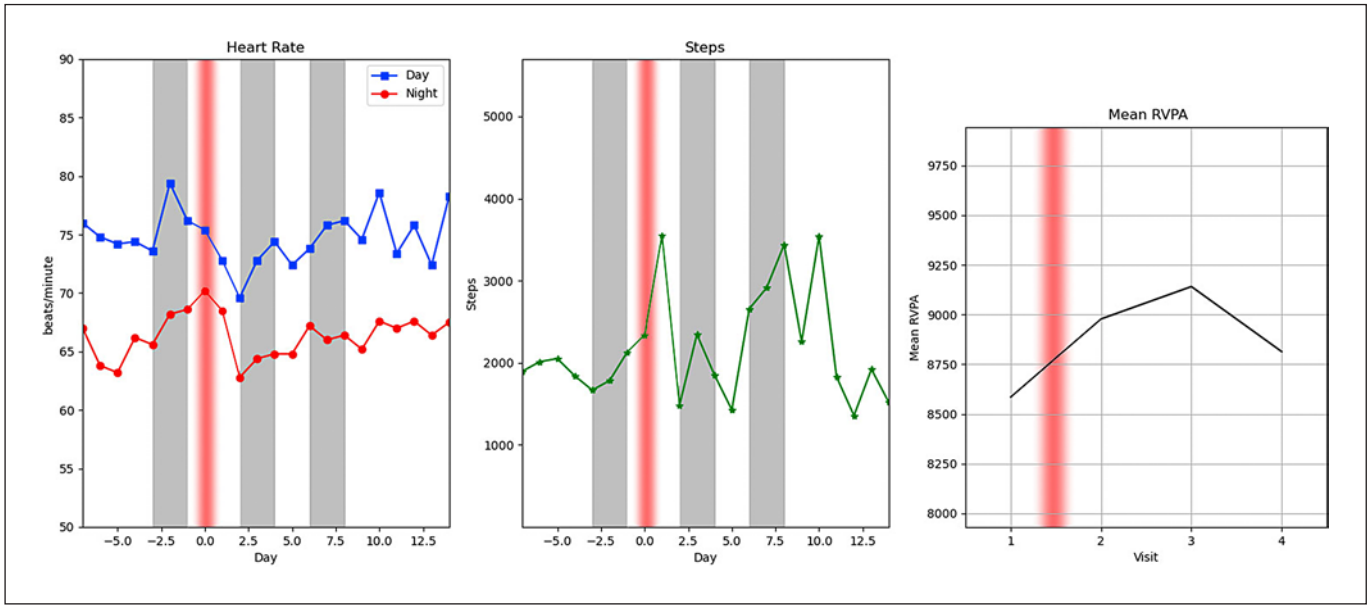

Fig. 4. Population changes of mean heart rate per day/night (left), mean steps per day (middle right) as measured by the Withings Steel HR, and RVPA (right). The RVPA is the main outcome of sustained attention as measured by the CANTAB RVP. Transfusion day results, indicated with the red zone, should be interpreted with caution because of their clear aberrance with normal at home days (outcomes per individual in supplementary material 2 and 3).

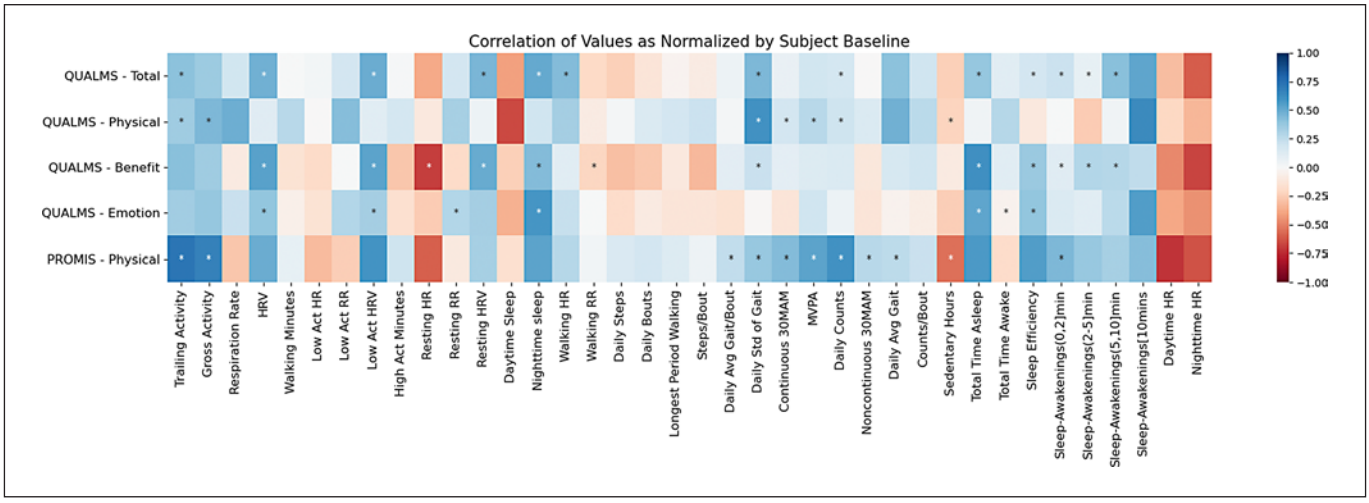

Fig. 5. Heatmap of Spearman correlation coefficients when comparing questionnaire responses to physiological features, as compared to a subject's baseline. Significant positive correlations are mostly activity-based, indicating that a patient is more likely to score higher on HR-QoL questionnaires when he/she is more active (significant correlations are indicated by * in the cells above).

ed objective physiological changes following RBC transfusion.

To further investigate how the physiological features are related to subjective quality of life metrics, spearman correlations were leveraged. We compared the change in physiological features to the change in questionnaire metrics at each visit from baseline. Changes in activity levels were identified as significantly correlated with changes in questionnaire responses more so than other physiological parameters (Fig. 5). The correlation coeffi-

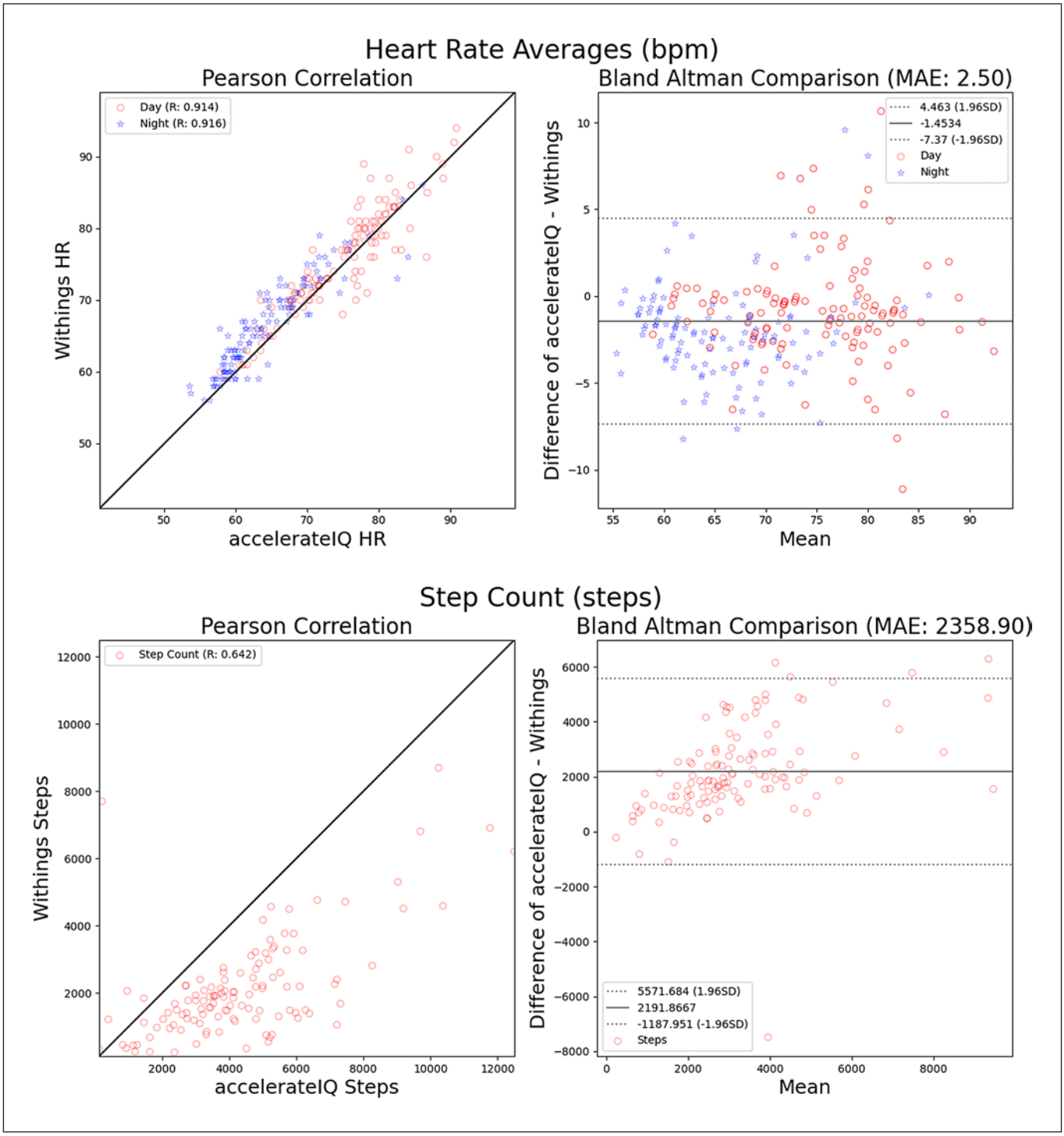

Fig. 6. Correlation plot and Bland-Altman analyses for comparing daily heart rate ($n = 238$ samples; upper graphs) and step counts ($n = 120$; lower graphs).

cients were positive, indicating that subjects identified an increase in QoL when there was an increase in activity levels. Furthermore, though not significant, a negative correlation was found between questionnaire metrics and heart rates, suggesting that patients are more likely to report higher QoL scores when having a lower heart rate.

VitalPatch-Withings Comparison

Both accelerateIQ and Withings produce a night-time resting and daily heart rate. To quantify similarities, Bland-Altman and Pearson correlation plots were leveraged. Overall, the mean absolute error is only 2.50 bpm (daily 2.23, nightly 2.76 bpm) where the accelerateIQ device tends to calculate a lower heart rate than Withings by more than 1 beat per minute (Fig. 6).

The correlations between step measurements, however, are less encouraging. The two devices had a mean absolute error of 2,359 steps. The accelerateIQ step count values were consistently higher than the Withings device on all subjects (Fig. 6).

Discussion

Key Findings

The present pilot study clearly validates the further use of wearables and data processing for larger cohort trials focussing on vital signs, activity, and cognitive performance as functions of the chronic red cell transfusion regimen. Data collection was without structural or troubling complications. In our group of just 5 patients, we found significant RBC transfusion-induced differences in cognition and heart rate. Low activity heart rate was clearly associated with the timing of RBC transfusion: a drop of ±7.15 bpm (p = 0.011) after RBC transfusion, which thereafter slowly returned to baseline. On the other hand, both the VitalPatch and the Withings watch did not show transfusion-induced changes in activity data. While the absence of intraindividual changes is not illogical for the short observation period, activity parameters may be usable for stratification and confounding purposes. With regard to cognitive performance, the CANTAB RVP task showed a significant reversible increase in sustained attention after RBC transfusion. In contrast, QoL questionnaires did not show any direct correlation to the RBC transfusions.

Strengths and Limitations

As an explorative pilot, the small number of patients obviously limits the value of transfusion-induced effects, and more detailed investigation is needed. Furthermore, numerous confounders potentially influenced the heart rate activity, stress, fluid intake, etc. This makes the exact effect of RBC transfusion on heart rate dynamics uncertain, as illustrated by the day-to-day variability in heart rate in Figures 3 and 4. A larger group of patients followed over more transfusion episodes should even out the influence of extremes in and between single patients. On the other hand, the use of a within-subject design also limits bias: fixed characteristics, both measured and unmeasured, cancel out by using patients as their own controls.

Although the Withings' Steel HR is not medically validated for measuring continuous heart rates, we chose to use this smartwatch together with the VitalPatch, to see if a photoplethysmography-based device could yield the same insight as an ECG-based biosensor. The Withings Steel HR heart rate data correlate well with the VitalPatch's data. Step count data, on the other hand, do not correlate well at all. It is not known if the Withings Steel HR step count algorithm has been validated against a ground truth reference. However, the accelerateIQ algorithm has been validated against reference data.

Interpretation

In terms of our primary objective, capturing usable data with these devices is certainly feasible. In view of the relevance of our data, the heart rate – although heavily confounded – showed a clear association with the RBC transfusions, as did sustained attention. These data support the logical assumption that an increase in haemoglobin concentration – and therewith oxygen transport capacity – by a RBC transfusion reduces the need for cardiopulmonary compensation, and thus results in a reduced heart rate. Likewise, the increase in oxygen transport capacity appears to have a beneficial effect on the patient's sustained attention. The fact that the haemoglobin concentration is only increased optimally once the excess plasma volume has been redistributed explains why we found the heart rate to be at its lowest 2–3 days post-transfusion. Significantly modulated in a group of 5 patients, heart rate and cognition seem very promising parameters to be further investigated in a larger group.

Being probably better associated with more structural and longer-standing changes in haemoglobin, neither quality of life nor activity parameters showed useful trends in our short follow-up study with only reversible haemoglobin improvement. It should, moreover, be noted that the present study was partly conducted during a COVID-19 lockdown, which undoubtedly decreased the patient's activity. Moreover, activity levels are heavily impacted by weather, lifestyle choices, and daily schedules, but also by the gradual building of fitness.

Zooming in on the usability of the data, the absolute value of steps data is uncertain, while also the accelerateIQ and Withings data show large differences. These findings, consistent with current literature, can be attributed to differences in device location, walking speeds, and

differences in algorithms [23–25]. Additionally, step counts are susceptible to high levels of noise and are challenging to ensure accurate counts. However, trends are comparable between devices. The absolute value of steps may be less important than the relative value, though, because we are interested in changes in activity, not the absolute number of steps. As there is no gold standard for step measurements to compare the devices to, it is difficult to confidently state which device – if any – is more accurate and able to detect meaningful change. It is important to realize, however, that we cannot compare data from different devices without a penalty.

Whether and how actigraphy can be used to measure substantial quality of life improvements remains an actual question [26–28]. A larger sample size and longer observation periods with structural improvement of anaemia should help to reduce confounding effects and improve the sensitivity for possible benefits of RBC transfusion modulation.

When choosing a device for remote monitoring, we advise to take into consideration the types of data streams that can be captured, device usability, data availability, and the data acquisition approach. In our study, we used accerateIQ™, which recorded a richer set of data types (respiratory rate, heart rate variability, and more) with higher granularity than the Steel HR. Capturing the high-fidelity multivariable data that accelerateIQ provides enables deeper exploration of parameters and the relationship with therapies, but at the cost of additional patient guidance and regular charging of the device, not necessarily required for a consumer device like the Steel HR with a battery life of ± 28 days.

When comparing the heart rate as captured by accelerateIQ to the Withings Steel HR, the outcome was similar. Small variations in the heart rate can be explained by differences in device location and algorithmic processing. In addition, neither device system yielded perfect subject compliance as occasional gaps of data were present – attributed to either the patients not wearing a device or struggling with connectivity issues. Depending on the objectives of the study, we found both devices to be usable for future studies.

Regarding generalizability, the present study focusses on patients with chronic anaemia due to a haematological disorder, which is a select group of patients that has been structurally excluded from previous studies. A well-designed larger study may yield generalizable results for this population.

In conclusion, in a 5-patient cohort of transfusion-dependent haematological patients we found that the accelerateIQ, Withings Steel HR and CANTAB platforms enable acquisition of high qualitative data. The device platforms identified a significantly and reversible decrease in heart rate and increase in sustained attention following RBC transfusions in this cohort. This feasibility study justifies larger validation trials to confirm that these wearables indeed can help to determine personalized RBC transfusion strategies and thus optimization of each patient's QoL.

Statement of Ethics

Ethical approval was granted by the Medical Ethics Committee Leiden-Den Haag-Delft, approval number: NL70534.098.19. The trial was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki 2013. Written informed consent was obtained from all participants before enrolment.

Conflict of Interest Statement

Mackenzie Tweardy and Stephan Wegerich are employees of physIQ, Inc. Rik Tonino, Martin Schipperus, and Jaap Jan Zwaginga have no conflicts to disclose.

Funding Sources

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Author Contributions

Rik Tonino, Martin Schipperus, Jaap Jan Zwaginga, and Stephan Wegerich conceived the study design. The study was carried out by Rik Tonino. Rolf Brouwer contributed patient inclusions. Rik Tonino and Martin Schipperus verified the underlying data and ran the statistical tests. All the authors participated in the interpretation of the results. Rik Tonino and Mackenzie Tweardy wrote the first draft. All the authors reviewed the draft.

Data Availability Statement

Individual participant data that underlie the results reported in this article will be available after deidentification (text, tables, figures, and supplementary material) in our University's data warehouse but without investigator support other than deposited metadata. Other documents that will be available are the study plan and statistical analysis plan. Data will be available following publication, no end date. It will be shared with researchers who provide an approved methodologically sound proposal. Further enquiries can be directed to the corresponding author. All data generated or analysed during this study are included in this article and its online supplementary material. A preprint version of this article is available on preprints.jmir.org [ref: 30895] [29].

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