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A feedback system that combines monitoring of systolic blood pressure and relative blood volume in order to prevent hypotensive episodes during dialysis

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ABSTRACT

Hypotensive Episodes (HEs) are one of the most common complications during dialysis. Occurrence of HEs can be reduced by applying physiological closed loop systems that monitor physiological parameter(s) and adjust dialysis related parameter(s). We developed a physiological closed loop control system (PCLCS) that monitors systolic blood pressure (sysBP) and relative blood volume (RBV) and calculates the net fluid removal (nfr) rate during dialysis. The performance of PCLCS was compared in the laboratory to a feedback system that monitors only RBV (BVFS). A laboratory test setup was developed to test the feedback systems. The test setup simulates nfr-rate and refilling of a patient's intravascular fluid. We studied the impact of the feedback systems PCLCS and BVFS on the number of HEs ($sysBP < 90$ mmHg), on the variance of sysBP and RBV, on pre to post sysBP and RBV and on the achievement of the nfr-volume. PCLCS allowed 80% less HEs than BVFS ($p < 0.001$). Variance of sysBP and RBV were reduced by 41.8% and by 52% ($p < 0.001$), respectively, when using PCLCS. There were no differences between pre to post sysBP nor between pre to post RBV when comparing PCLCS to BVFS. The nfr-volume was achieved by both feedback systems.

List of Abbreviations and Nomenclatures

Abbreviation	Nomenclature	Description
BV	Blood Volume	Volume of blood in a dialysis patient including water intake in the inter dialysis time
BVFM	Blood Volume Fuzzy Module	A foundation of the Blood Volume Fuzzy System that evaluates the slope of the relative blood volume
BVFS	Blood Volume Fuzzy System	A feedback system which evaluates the slope of the relative blood volume to calculate a net fluid removal rate
HCT	Hematocrit	The fraction of cellular components in the blood
HE	Hypotensive Episode	A drop in blood pressure accompanied with adverse events such as headache and muscle cramps
LTFM	Long Time Fuzzy Module	A foundation of the Physiological Closed Loop Control System PCLCS that evaluates the long term progression of systolic blood pressure
nfr	Net Fluid Removal	The fluid withdrawn through the dialyser during a dialysis treatment
NFRFM	Net Fluid Removal Fuzzy Module	A foundation of the Blood volume Fuzzy System BVFS and the Physiological Closed Loop Control System PCLCS that calculates the net fluid removal rate
PCLCS	Physiological Closed Loop Control System	A feedback system which evaluates the slope of the relative blood volume and the progression of the systolic blood pressure to calculate a net fluid removal rate
RBV	Relative Blood Volume	A variable that mirrors the percentage of blood volume reduction during a dialysis treatment
STFM	Short Time Fuzzy Module	A foundation of the feedback system PCLCS that evaluates the short term progression of systolic blood pressure
sysBP	Systolic Blood Pressure	The pressure of blood applied on the walls of an arterial blood vessel

Note: Mathematical variables used in this work are not considered in this list of abbreviations

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1. Introduction

Hypotensive episodes (HEs) are one of the most common complications of dialysis. They occur in 25% to 55% of treatments and are often causally followed by cramps (up to 20%), nausea and vomiting (5–15%), headache (5%), chest and back pain (2–5%), itching (5%) and fever and chills (1%) [1,2]. HEs do not only increase morbidity and reduce quality of life of patients with chronic kidney disease [3] but are even an independent risk factor for mortality [4,5].

An HE is a reduction in blood pressure associated with adverse events [6,7]. The Kidney Disease Outcomes Quality Initiative (KDOQI) [6] defines an HE as a decrease in systolic Blood Pressure (sysBP) greater than 20 mmHg or a decrease in mean arterial blood pressure by 10 mmHg associated with symptoms such as abdominal discomfort and vomiting. However, there is no consensus in literature on the definition of an HE and various alternatives have been proposed (*e.g.* $sysBP \leq 90$ mmHg if pre dialysis $sysBP \geq 100$ mmHg) [8,9].

It is well reported that hypovolemia is the main initiator of HE [10–12]. It is a consequence of an exceeding rate of water removal during the dialysis treatment [13]. Initially, the patient's compensatory mechanisms seek to prevent this hypovolemia. However, these compensatory mechanisms seem to be impaired in a large population of dialysis patients, which induces HEs [14].

The past 20 years have seen rapid advances in the development and use of techniques, such as bioimpedance spectroscopy [15–17] and feedback systems [3,18,19] that aim to monitor hemodynamic instability and detect or prevent HEs. These techniques monitor dialysis-related physiological and hemodynamic parameters (*e.g.* hematocrit (HCT) or blood temperature) to adjust machine-related parameters (*e.g.* net fluid removal (nfr)-rate or dialysate conductivity).

It has been demonstrated that the majority of feedback systems increase quality of life and reduce HEs by up to 39% [8,9,20–22]. However, all these systems monitor a single physiological parameter, either relative blood volume (RBV) or sysBP. Feedback systems that are based on sysBP limit patient comfort because of frequent measurements of sysBP (up to 48 measurements during a 4 h dialysis treatment [23]). Systems based on RBV may induce a needless reduction of the control variable (*e.g.* nfr-rate) since reduction in RBV is not always related to the incidence of HEs [24–26].

In this article, we perform a laboratory-based comparison of the performance of two new feedback systems based on fuzzy logic. First, a Blood Volume Fuzzy System (BVFS) continuously monitors RBV to adjust the nfr-rate; second a Physiological Closed Loop Control System (PCLCS) integrates sysBP monitoring with BVFS. Since PCLCS continuously monitors RBV, it can limit sysBP measurements to only 10 times during a regular dialysis treatment, and thus increases patient comfort without compromising functionality.

Due to the inter- and intra-individual variability of dialysis patients, we used the input of data from dialysis treatments, physicians and nephrologists to define the ranges of the membership functions (fuzzy sets) for all input and output variables of BVFS and PCLCS.

2. Materials and methods

2.1. The feedback systems

2.1.1. Architecture of BVFS

Fig. 1 depicts the architecture of BVFS. BVFS consists of two fuzzy modules: Blood Volume Fuzzy Module (BVFM) and Net Fluid Removal Fuzzy Module (NFRFM). BVFM evaluates the slope of RBV in five-minute intervals as input. The slope of RBV is approximated by using a linear least square fit over the last ten minutes of RBV values and is calculated in $\%/h$. As output, BVFM calculates a sensitivity value, the hyporelevance (*hre*), which describes the probability of an HE between 0 and 100 %. The higher the value of *hre*, the more the patient is likely to undergo an HE.

hre and the ratio of the current and the desired net fluid removal volume constitute the input of NFRFM, which calculates the final output, the nfr-rate. As described by Mancini *et al.* [8], the nfr-rate calculated by BVFS at stable RBV starts with high nfr-rates (up to 200% of the average nfr-rate) at the beginning of the treatment and remains constant until 65% of the nfr-volume are achieved. It then decreases until 85% of the total nfr-volume are achieved and remains constant until the end of the dialysis session.

2.1.2. Architecture of PCLCS

Fig. 2 depicts the architecture of PCLCS. PCLCS integrates BVFS with two fuzzy modules that evaluate sysBP. First, the Short Time Fuzzy Module (STFM) evaluates sysBP in five-minute intervals (measured and calculated sysBP). It is important here to remember that the number of measured sysBP by PCLCS is limited to 10 during a regular dialysis treatment. The calculated sysBP is based on a prediction algorithm described by Roeher et al. [27]. STFM is adopted from an already existing feedback system presented by Schmidt et al. [28] and Mancini et al. [8]. Second, the Long Time Fuzzy Module (LTFM) evaluates only measured sysBP over the last 120 min. Similar to BVFM, the input variables of STFM and LTFM are fuzzified with pre defined fuzzy sets. The defuzzification of these input variables uses the COA method and results each in an *hre* value to indicate risk of HE. The output of each STFM, LTFM and BVFM is combined in a weighting unit into a final *hre* value. In analogy to BVFS, *hre* and the ratio of the current and the desired nfr-volume constitute the input of NFRFM, which calculates the final output, the nfr-rate. The nfr-rate profile calculated by PCLCS at stable sysBP and RBV is identical to the profile calculated by BVFS.

2.1.3. Input variables of PCLCS

STFM evaluates the trend of sysBP over up to 30 min by using three variables, *rbd, htr* and *ada*, based on measured and calculated sysBP. A detailed description of STFM is presented by Schmidt et al. [28] and Mancini et al. [8].

The variable *rbd* analyses the relative distance between the current sysBP ($sysBP_i$) and a systolic limit *(sll)* defined by medical staff. The *rbd* is calculated from $sysBP_i$ and sp, where sp is 1.25 times sll.

$$rbd = \frac{sp - sysBP_i}{sp} \tag{1}$$

The variable *htr* is a short time trend of sysBP based on sysBP values in an interval of 15 min. The variable *htr* gives information about the patient's short time sysBP stability. It is calculated as follows:

$$htr = \left(\frac{1}{2} \sum_{i=-3}^{-2} sysBP_i \right) - sysBP_{i=0} \tag{2}$$

where i is the index of sysBP measurement. $i = 0$ corresponds to the current sysBP value.

The third input variable of STFM is *ada*. The variable *ada* describes a long time trend over the last five sysBP values, *i.e.* it reflects the sysBP behavior of the patient over the last 25 min. The variable *ada* is calculated as follows:

$$ada = \frac{1}{6} * \Big(sysBP_{i-5} + 2 * sysBP_{i-4} + sysBP_{i-3} - sysBP_{i-2} - 2 * sysBP_{i-1} - sysBP_i \Big)$$

LTFM evaluates three input variables that are calculated from measured sysBP. A first input variable, blood pressure difference

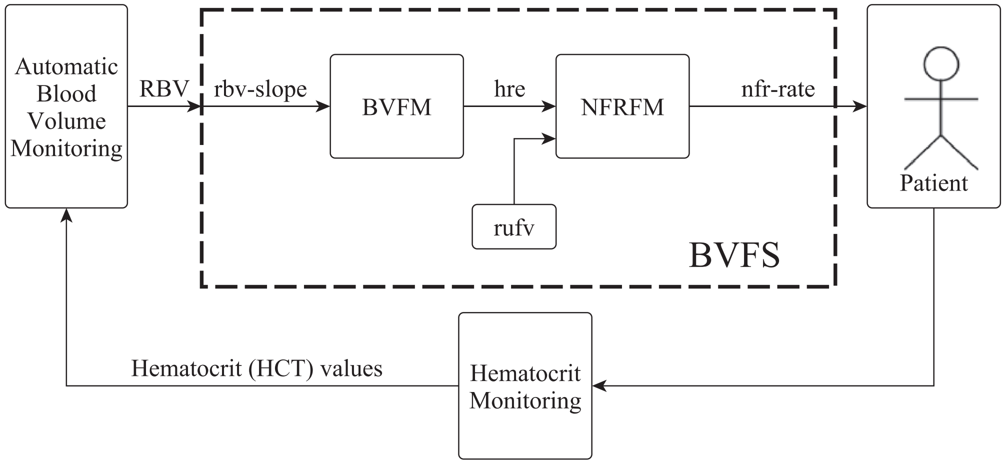

Fig. 1. Architecture of BVFS. BVFM uses one variable as input that is calculated from RBV values. BVFM calculates a sensitivity value, the hyporelevance (*hre*) in 5-min intervals. Together with the ratio of the current and the desired nfr-volume (rufv), *hre* constitutes the input of NFRFM. This module calculates the current desired nfr-rate.

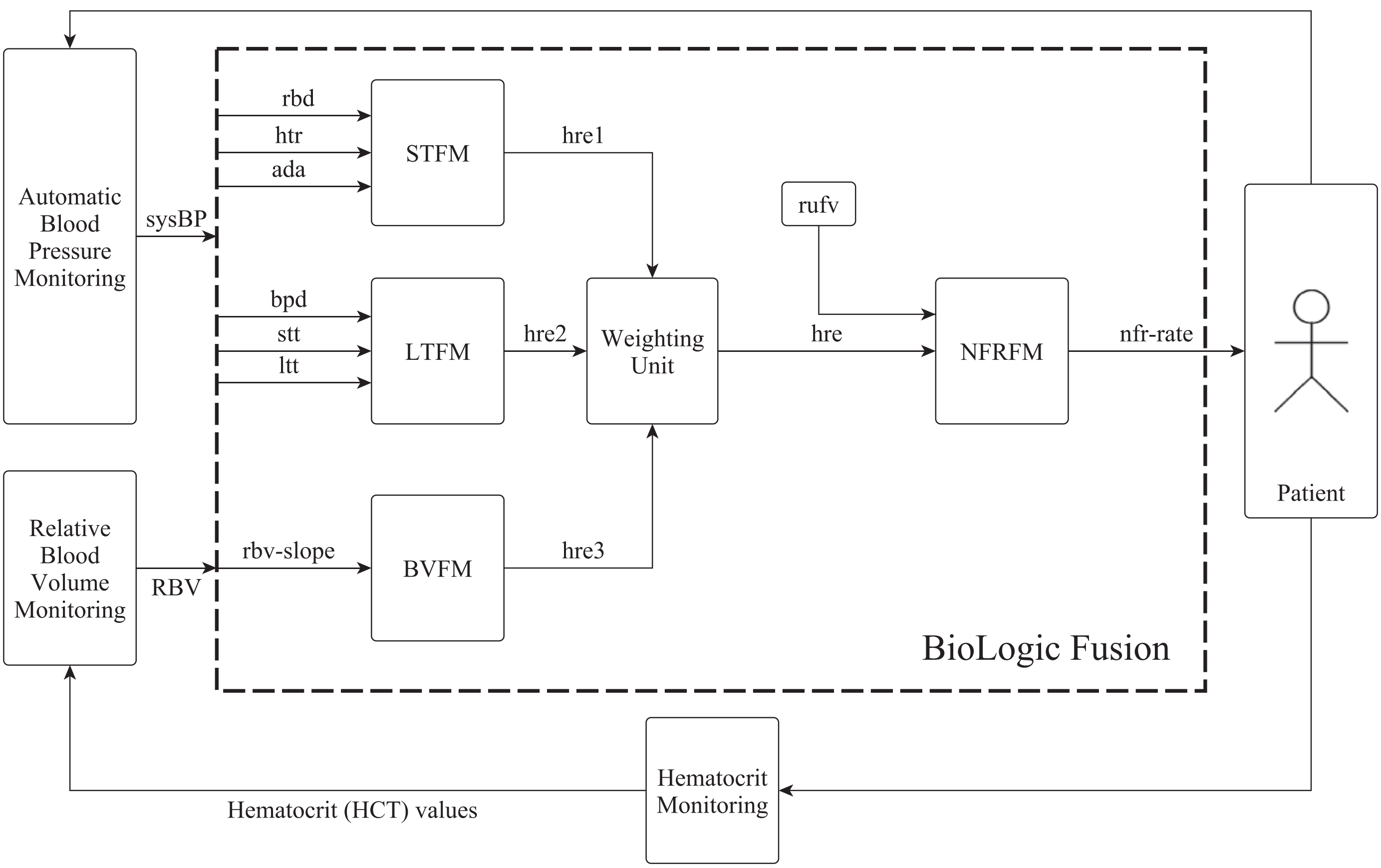

Fig. 2. Architecture of PCLCS. STFM and LTFM use six variables as input that are calculated from sysBPs (measured and/or calculated by a prediction algorithm [27]). BVFM uses one variable as input that is calculated from RBV values. Each of these modules calculates a sensitivity value in five-minute intervals. These sensitivity values are processed in a weighting unit into a combined *hre*. Together with the ratio of the current and the desired nfr-volume, *hre* constitutes the input of NFRFM. This module calculates the current desired nfr-rate.

(bpd), is defined to detect sharp drops in sysBP. This variable is calculated as the difference between the two most recently measured sysBPs:

$$bpd = sysBP_i - sysBP_{i-1} \tag{3}$$

The second and third input variables of LTFM, short time trend *(stt)* and long time trend *(ltt)* reflect the short and long time trend of measured sysBP. The values of *stt* and *ltt* are calculated by a linear least squares fit over the last three and last five measured BPs, respectively.

$$stt = sysBP_{fit_i} - sysBP_{fit_{i-2}} \tag{4}$$

$$ltt = \begin{cases} sysBP_{fit_i} - sysBP_{fit_{i-3}}, & \text{for } n = 4, \\ sysBP_{fit_i} - sysBP_{fit_{i-4}}, & \text{for } n \geq 5 \end{cases} \tag{5}$$

$sysBP_{fit_i}$ is the sysBP value on the linear least square fit corresponding to the time when $sysBP_i$ is sampled.

The input variable of BVFM is the same used in BVFS (see Section 2.1.1).

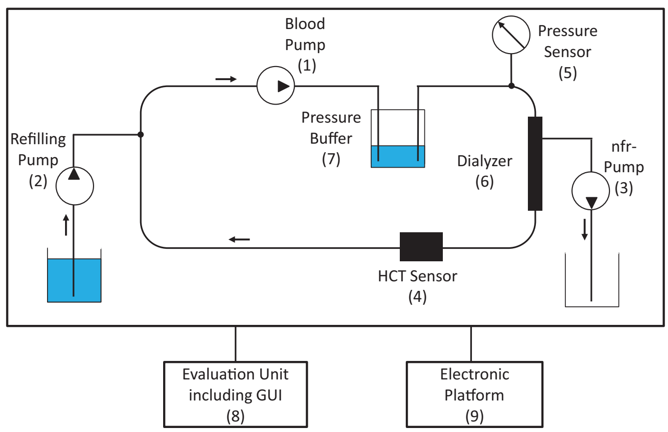

Fig. 3. *In-vitro* test setup that simulates a dialysis treatment and the fluid status of the patient during the treatment. The test setup uses a blood pump (1), refilling (2) and nfr (3) pumps, an HCT (4) and pressure (5) sensor, a dialyser (6), a pressure buffer (7), a GUI (8) and an electronic platform (9).

2.2. Laboratory test setup and experiments

To compare the performance of PCLCS and BVFS in the laboratory, a test setup was developed, which simulates the fluid status of the patient during a dialysis treatment.

Fig. 3 shows the *in-vitro* test setup. The test setup represents two compartments of the body: the intra vascular and the extra vascular compartment. During a treatment performed with the test setup, a blood pump (1) (peristaltic, 30–600 ml/min ± 10%) continuously circulates bovine blood or sodium chloride solution (0.9 %, osmolarity 308 mOsm/l, pH 4.5–7.0, temperature 37 °C in a closed circuit (curved silicon rubber tube) at a temperature of 37 °C with a speed of 300 ml/min. The feedback systems evaluate with the help of a pressure sensor (5) (−650 mmHg – +750 mmHg ± 10 mmHg) and/or an HCT sensor (4) (electromagnetic radiation, 805 nm, 1450 nm and 1550 nm, HCT range 20–50%) the circuit pressure (representing sysBP) and RBV, respectively, and calculate an nfr-rate. This nfr-rate is applied to a nfr-pump (3) (piston pump, 50 ml/h – 4000 ml/h ± 1 %) that withdraws the calculated nfr-rate from a dialyser (6). The patient's refilling rate is simulated by a refilling pump (2) (piston pump, 50ml/h–4000 ml/h ± 1 %). This pump delivers pre-defined refilling rates, as described in the next paragraph. To avoid large changes in circuit pressure that are caused by small differences of the refilling and the nfr-rate, a pressure tight fluid reservoir acts as a pressure buffer (7). The components of the test setup are controlled via a GUI written in MATLAB (8) (R2014b, The MathWorks, Inc., USA) that communicates with two mbed development platforms (ARM, UK) (9) [29] to read data from HCT and pressure sensors, and to control the refilling and nfr-rate.

Refilling rate. During a regular dialysis treatment, water shifts between the extra vascular and intra vascular compartment. We modelled this shifting process (refilling) in our test setup according to the results of Rouby et al. [30] and recent work by Thijssen et al. [31]. The authors reported that RBV is related to the difference of the nfr- and the refilling rate. This finding was supported by Lopot et al. [32], who described the change in absolute blood volume (∂bv) over time (∂dt) as follows:

$$\frac{\partial bv}{\partial t} = \textit{nfr-rate} - \textit{refilling rate} \tag{6}$$

The withdrawn blood volume Δbv from the beginning of the treatment until the current point of time t during the treatment

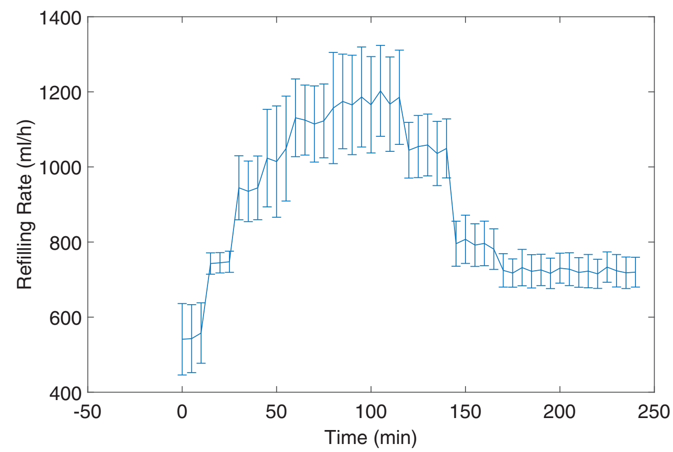

Fig. 4. Average refilling rates calculated by applying Eq. (9) to data sets 93 dialysis treatments.

can be deduced from RBV as follows [33]:

$$rbv_t = \left(\frac{bv_t - bv_{t0}}{bv_{t0}}\right) * 100 \Longrightarrow \Delta bv = \frac{bv_{t0} * rbv_t}{100} \tag{7}$$

bv_{t0} is the total absolute blood volume at the start of the therapy, bv_t and rbv_t are the current absolute blood volume and current RBV at time t during the treatment, respectively. $\Delta bv = bv_t - bv_{t0}$ is negative when rbv_t is negative, which is the most likely case during a dialysis therapy.

Thus, the change in blood volume in a time interval $\Delta t = t - t_{-1}$ during the treatment can be calculated as

$$\begin{aligned} \frac{\Delta bv}{\Delta t} &= \frac{bv_t - bv_{t_{-1}}}{\Delta t} \\ &= \frac{bv_{t0} + \left(\frac{bv_{t0}}{100} * rbv_t\right) - bv_{t_{-1}}}{\Delta t} \\ &= \frac{bv_{t0}\left(1 + \frac{rbv_t}{100}\right) - bv_{t_{-1}}}{\Delta t} \end{aligned} \tag{8}$$

$bv_{t_{-1}}$ is the remaining blood volume at the beginning of the time interval Δt. This means that $bv_{t_{-1}}$ equals bv_t calculated in the previous iteration. Due to the fact that the change of blood volume over time is calculated in five-minute intervals for the experiments, we used $\frac{\Delta bv}{\Delta t}$ to approximate the differential $\frac{\partial bv}{\partial t}$ described by Lopot et al. [32].

The average refilling rate was calculated from RBV and nfr-rate data of 93 treatments performed with a sysBP based feedback system described by Schmidt et al. [28], by combining Eqs. (6)–(8):

$$\textit{refilling rate} = \textit{nfr-rate}_{t_{-1}} - \left(\frac{bv_{t0}\left(1 + \frac{rbv_t}{100}\right) - bv_{t_{-1}}}{\Delta t}\right) \tag{9}$$

$nfr\text{-}rate_{t_{-1}}$ is the nfr-rate applied at the beginning of the time interval Δt, which is based on the application of the fuzzy systems to data from the time interval leading up to t_{-1}. This nfr-rate is not changed until the end of the time interval. In absence of data for each individual patient, we assumed bv_{t0} equals 5000 ml, which was also used in our experiments as initial blood volume.

Fig. 4 represents average refilling rates of 93 treatments. This figure shows that the refilling rate starts with low refilling values until it achieves a maximum at approx. 1/3 of the dialysis time. The refilling rate then decreases and takes quasi constant values from about minute 150 until the end of the treatment. This behaviour of the refilling rate over time was taken as the basis for modeling the refilling rate in our experiments. To simulate intra individual variability in the refilling rate during a dialysis treatment, a random component within pre defined limits (± 300 ml) was added to the average refilling rate at each interval Δt. The range was chosen based on the variation of the refilling rates of the 93 treatments.

Experimental implementation of changes to RBV:
during the experiments, bovine blood deoxygenated and often hemolysed after a limited number of treatments, which made RBV values unreliable. This made it difficult to use bovine blood to test the feedback systems. However, RBV constitutes an essential input for PCLCS and BVFS, and needs to be available for the experiments.

A particularity of our test setup is that RBV is only a function of the refilling and nfr-rate. Therefore, RBV can be calculated from Eq. (9) if the refilling and nfr-rates are known. To validate this calculated RBV, we performed 10 consecutive treatments using bovine blood. In this validation we measured RBV using the HCT sensor as shown in Fig. 3 and simultaneously calculated RBV using Eq. (9). Comparing measured and calculated RBV, the correlation coefficient R was 0.95. The root mean square error (rmse) between the mean measured and the mean calculated RBV equaled 3.8%. Dasselaar et al. showed a similar rmse of RBV curves of 7 stable patients that equaled 3.7% [34]. As a consequence, the high R of 0.95 and the low rmse of 3.8% resulted by calculation instead of measurement of RBV are acceptable. This allowed us to calculate RBV with Eq. (9) and to replace bovine blood with sodium chlorid solution (0.9%, 308 mOsm/l, pH 7.4, temperature 37 °C) in our experiments.

Experiments:
for the validation, two types of treatment were performed with each of PCLCS and BVFS. First, we performed 25 regular treatments. In these treatments HEs occur as consequence of the mismatch between refilling and nfr-rate, and always coincide with a decrease in RBV. These experiments therefore represent the case that an HE is associated with drops in RBV [35]. The 25 regular treatments were followed by 25 treatments where an HE was induced by a system pressure decrease without changing RBV. This represents the case in literature where RBV does not predict HE [11,36]. The system pressure decrease was achieved by withdrawing 20 ml of air from the pressure buffer (7) at minute 80 with a syringe. In this way, we induced a pressure drop of approx. 15 mmHg in the set up while RBV was unaffected. The withdrawn air volume was given back to the system at minute 200. In these treatments, HEs may still occur as a consequence of the mismatch between refilling and nfr-rate. Further, it is important to mention that the same refilling profiles were applied to each of PCLCS and BVFS to provide identical refilling input.

In order to perform these experiments in a time efficient way, the time base of the treatment and of the feedback systems was reduced by a factor of 10. All actions performed in the regular systems in 5-min intervals are performed in 0.5-min intervals in these experiments. In practice, this means that the feedback systems calculate an nfr-rate and apply a refilling rate every 30 s. During this time, the nfr and refilling pump run with the rates calculated by the feedback systems in the last iteration. When the 30 s have passed, the feedback systems calculate a new nfr-rate, just as they would if the regular 5 min had elapsed. As a consequence of this procedure, the treatment time in our experiments equaled 24 min instead of 240 min in a typical dialysis therapy, and the withdrawn nfr-volume, amounted to 400 ml, a factor of 10 lower than in a typical dialysis therapy. For display of results, the time scale was re-normalised by multiplication of 10. The initial circuit pressure equaled 130 mmHg, which is the average pre-dialysis sysBP in dialysis patients [35]. In case of disturbances, *e.g.*, blocked piston pump, the experiment was interrupted and completely repeated after solving the problem. Only non-perturbed experiments were taken into consideration in our evaluation.

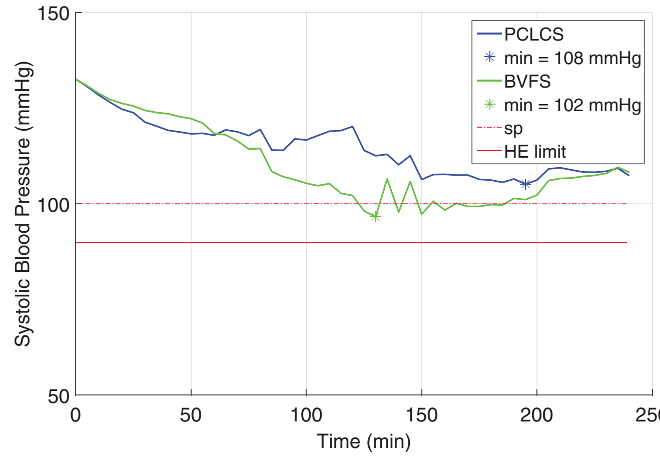

Fig. 5. Mean sysBP as a function of time over all experiments of each feedback system. Time scale was re-normalized by a factor of 10. Both Mean sysBP curves did not violate HE limit of 90 mmHg. However Mean sysBP in experiments with PCLCS did not violate *sp* (set point), a close limit to an HE that is used by PCLCS, whereas it did several times in experiments with BVFS.

Evaluation parameters:
the following criteria were taken into consideration to assess the performance of the feedback systems:

- Number of HEs: an HE is defined as a drop in sysBP value below 90 mmHg [8] during our experiments.
- Stability of sysBP and RBV: stability of sysBP and RBV is calculated using the average of the variance of sysBP and RBV for all treatments of each feedback system. The lower the variance, the more stable sysBP and RBV.
- Pre and post dialytic sysBP and RBV: the average of the difference between first and last measured sysBP and RBV is calculated for all treatments of each feedback system.
- Achievement of the nfr-volume: the difference between the desired and the achieved nfr-volume is calculated for each treatment.

2.3. Statistical analysis

All data were analysed by using MATLAB R2014b (The MathWorks, Inc., USA). Comparison of the evaluation parameters was performed with the Wilcoxon signed rank test. Unless otherwise stated, data are expressed as mean ± SD. p values were considered significant at a level < 0.05.

3. Results

Before presenting the results for the two feedback systems, it is interesting to take a look at the time series of the average sysBP in experiments run with PCLCS and BVFS. These are represented in Fig. 5. In the first 65 min, the mean sysBP of both systems shows a similar, slightly decreasing trend. From minute 65, sysBP controlled by PCLCS stabilises and never violates *sp* (100 mmHg, a close limit to an HE that is used by PCLCS), whereas sysBP controlled by BVFS further decreases until it violates *sp* at minute 125. The reason for this is that PCLCS timely reduces the nfr-rate when sysBP decreases, which limits the decrease in sysBP, whereas BVFS only reacts to changes in RBV and ignores sysBP. However, from minute 150, sysBP slightly re-increases in both systems due to the descending profile of the nfr-rate described in the introduction.

Table 1 shows the values of the evaluation parameters. The number of HEs was significantly reduced by 80% from 70 to 14 when using PCLCS instead of BVFS ($p < 0.01$). Furthermore, treatments performed with the PCLCS achieved more stable sysBP and

Table 1
Number of HEs and mean values of the evaluation criteria for treatments with each feedback system. Significance is calculated by using the signtest.

Evaluation criteria	BVFS	PCLCS	p value
Number of HEs (sysBP ≤ 90 mmHg)	70	14	0.0042
sysBP variance (mmHg^2)	132.2 $\pm$ 43.7	76.9 $\pm$ 30.5	<0.001
RBV variance (%^{2})	9.2 $\pm$2.6	4.4 $\pm$ 1.1	<0.001
pre to post sysBP (mmHg)	24.3 $\pm$ 5.2	25.2 $\pm$ 6.3	n.s
pre to post RBV (%)	8.8 $\pm$ 1.3	8.7 $\pm$ 1.3	n.s
Δ nfr-volume (ml)	0	0	n.s

RBV (variance of 132.2 ± 43.7 mmHg^2 vs. 76.9 ± 30.5 mmHg^2 for sysBP, $p < 0.001$, and 9.2 ± 2.6 %^{2} vs. 4.4 ± 1.1 %^{2} for RBV, $p < 0.001$). In contrast, there is no significant difference between pre to post parameters (24.3 ± 5.2 mmHg vs. 25.2 ± 6.3 mmHg for sysBP and 8.8 ± 1.3 % vs. 8.7 ± 1.3 % for RBV). The nfr-volume was achieved in both feedback systems.

4. Discussion

We aimed in this work to compare the performance of two new feedback systems in the laboratory. One feedback system calculates an adequate nfr-rate by evaluating sysBP and RBV. The other feedback system calculates an adequate nfr-rate by evaluating only RBV.

Our laboratory test setup was developed to simulate the fluid status of the patient during a dialysis treatment and to approximate outputs (*e.g.*, sysBP) of patients in regular dialysis treatments. We found in all tested systems a mean sysBP decrease at the end of the treatment of 24.8 mmHg with a standard deviation of 5.8 mmHg. These results are similar to the data presented by other authors in their studies on dialysis patients [37,38]. For example, Garzoni et al. [37] reported a reduction of sysBP by 18.8 mmHg with a large standard deviation of 26.7 mmHg. The mean sysBP decrease in our experiments of 24.4 mmHg is slightly larger than the value reported by Garzoni et al., however, it lies well within the reported standard deviation of 26.7 mmHg.

Schmidt et al. [28] reported the frequency distributions of $sysBP < 90$ mmHg over dialysis time. They reported a low frequency of $sysBP < 90$ mmHg at the beginning of dialysis treatment, a high frequency in the middle and a low frequency at the end of treatment when using a feedback system. These findings are also supported by the results shown in Fig. 5, which demonstrate that sysBP most often decreases in the middle and stabilises at the end of treatment. We believe that the reason for this is related to the high nfr-rates at the beginning and the low nfr-rates at the end of the treatment used by our feedback systems and by the feedback system described by Schmidt et al. [28]. We conclude that the experiments with the laboratory test setup approximate well the progression of sysBP reported by Schmidt et al. [28].

The *in-vitro* validation shows a large reduction of the number of HEs (−80%) when comparing PCLCS to BVFS. The main reason for this reduction is related to the direct monitoring of sysBP by the PCLCS. Due to the fact that PCLCS monitors the trend of sysBP over up to the last five measured sysBP, and keeps a watchful eye on the distance of current sysBP to *sp*, sysBP is timely controlled by reducing the nfr-rate. This timely reduction prevents sysBP to violate *sp*, and thus prevents an HE. This is an advantage over RBV-based feedback systems, as RBV is only an imperfect indicator of sysBP. The timely reaction of the nfr-rate to trends of sysBP and RBV also keeps sysBP and RBV more stable when using PCLCS. This is mirrored by the lower variances of both sysBP and RBV (variance reduction by −42 mmHg^2 for sysBP and by −52%^{2} for RBV). In contrast, both BVFS and PCLCS achieved similar pre to post sysBP and RBV. One possible explanation for this result is related to the profile of the nfr-rate used by both PCLCS and BVFS. This profile starts with high nfr-rates and ends with low nfr-rates. The low nfr-rate toward the end of each experiment seems to generate similar levels of sysBP in both feedback systems.

As far as we know, to date, no *in-vitro* validation of a feedback system exists with which we can compare our results. However, there are a number of clinical studies which compare treatment of patients performed with feedback systems to treatment of patients performed with constant nfr-rate. Unfortunately, we were not able to perform measurements with constant nfr-rate in the laboratory due to lack of data from which to calculate the refilling profile. This would have facilitated comparison of our laboratory data to that of the clinical studies. However, we are still able to draw conclusions when comparing our results with results of clinical studies that tested feedback systems on dialysis patients. Using an RBV-based feedback system, *Santoro et al.* showed a reduction of HEs by −30% when compared to treatments performed with constant nfr-rate (23.5% vs. 33.5%) [22]. A similar investigation on another RBV based feedback system presented by Gil et al. [38] showed a reduction of HEs by 42.2% when comparing to dialysis treatments with constant nfr-rate. A further investigation performed by Mancini et al. demonstrated a reduction of HEs by −39% when treating patients with a sysBP based feedback system (HEs equaled 8.3%) compared to when treating with constant nfr-rate (HEs equaled 13.8%). Due to the fact that our BVFS is an RBV based feedback system, at least similar results as the ones presented by Santoro et al. are expected when comparing to treatments with constant nfr-rate. According to our results, PCLCS, which is a feedback system based on both sysBP- and RBV-control, provides better results than RBV-based feedback systems. In fact, PCLCS reduced the occurence of HEs in our experiments by 80% compared to BVFS. Even if this reduction might not be achieved to its full extent in the clinical setting, this still constitutes a large improvement over existing technologies. Mancini et al. also reported that the nfr-volume was achieved in 100% of treatments. We obtained similar results since the nfr-volume was achieved in all treatments when using either PCLCS or BVFS.

We demonstrated in this work that our experiments achieved similar results (*e.g.*, pre to post sysBP and RBV and $\Delta nfr-volume$) to those reported by several publications. Nonetheless, we believe that our results are still affected by one main limitation. We defined an HE as $sysBP < 90$ mmHg based on several authors' suggestions [8,9,28]. However, these authors include more than one definition for an HE in their studies. They also define an HE, for example, as *any sysBP reduction* $\geq$*25mmHg compared to the pre-dialysis value, in the presence of symptoms and therapeutic manoeuvres* [9]. Simulating symptoms and therapeutic manoeuvres was not possible in our test setup. This different definition of an HE may give rise to a different number of HEs and thus to different results.

Furthermore, we are aware that intermittent measurements of sysBP in PCLCS constitute a serious limitation to continuously monitor patient's stability and to increase patient's comfort. On the other hand, it is well established that respiration has a direct impact on blood pressure measurements [39,40], and thus on the accuracy of the slopes of sysBP used as input into the algorithm. However, using intermittent blood pressure measurement and taking particularly sysBP as a marker for an HE was based on two major reasons: first, our PCLCS is based on an existing feedback system presented by Schmidt et al. and Mancini et al. that uses sysBP as input [8,28]. Second, an HE is represented in several works as a decrease in sysBP below a predefined limit [8,9,13]. Thus, we used sysBP as marker for an HE as input into PCLCS.

To date, several techniques allow continuous non-invasive measurements of cardiac related parameters such as blood pressure, heart rate or total peripheral resistance [41,42] and which were intensively used to assess hemodynamic dependencies [43,44]. However, these techniques have still not been established in dialysis routine. Thus, we strongly suggest to adapt feedback systems to be able to continuously evaluate cardiovascular parameters as soon as continuous cardiovascular monitoring becomes familiar in dialysis routine.

5. Conclusion

Based on the results of our experiments, we conclude that monitoring two physiological variables (*i.e.* sysBP and RBV) is able to reduce and better prevent HEs than monitoring only one physiological variable (*i.e.* RBV). Nonetheless, a clinical validation of our feedback systems is advised, to study the magnitude of HE reduction when these feedback systems are applied in the clinical setting.

Declarations

Competing interests: None declared.

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Ethical approval

None.

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