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Integrated Monitoring for Personalized Renal Replacement Therapy

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Abstract

Introduction: Emerging renal support devices tend towards automated physiological monitoring and treatment adaptation. In the patient-centred development of the mobile NEPHRON+ system decisive physiological aspects and their mutual affections were identified and methods of measurement were incorporated into a wearable system enabling a personalized and un-supervised auto-adaptive treatment.
Methods: Nephrologists determined the physiological variables to be monitored in dialysis patients. The experts' opinions were confirmed by extensive literature survey to find formalized relationships between the physiological parameters. As a basis for the embedded device control, suitable means of monitoring were integrated into the prototype of NEPHRON+, a networked mobile dialysis system.
Results: To monitor the principal function of the blood cleansing device, ion selective and enzymatic electrodes tailored towards the miniaturized device are integrated in the mobile blood treatment system. Weight measurements are transmitted via Bluetooth to gauge the hydration surplus to be removed. Both, fluidic and chemical dynamics in the body are described based on the measurements using compartment models.
Hemodynamic instabilities frequently arise during blood cleansing treatment due to homeostatic imbalance. Thus an electric sphygmomanometer and heart rate acquisition are likewise connected for intermittent measurements. To interpret these context sensitive parameters an accelerometer is embodied into the wearable system enabling to estimate the influence of the treated patient's physical activity on aforementioned vital parameters. This allows differentiating between the vital parameter dynamics arising from activity and the negative influence of homeostatic imbalance.
Conclusion: A prototypic architecture for a defined treatment scenario has been realized to demonstrate the technical feasibility, enabling comprehensive physiological monitoring of dialysis treatments. Mathematical models of the monitored variables were gleaned for context aware evaluation of the mutually dependent parameters.

1 Introduction

An increasing number of patients with renal failure are treated outside of a clinical setting. Conventional hemodialysis is supervised by medical experts who monitor the patient during the treatment. Based on such an analysis of physiological parameters they adapt the function of the device, to provide an appropriate treatment. Especially when such treatments are conducted in a home environment, dialysis devices should be equipped with means of automatic control to provide personalized treatment. [1]
Parameters to be monitored range from chemical composition of the blood up to vital signs, which are indirectly affected by the treatment. However, to comprehend the physiological status of the patient it is not sufficient to apply different measurements. Moreover it is important to take into account interactions between the parameters, as done by a medical expert. This cognitive process of decision making cannot straightforwardly be emulated in a device. A formalized model of the patient under treatment is one way to enable an automatized combined analysis of measurements and the interdependencies between the different parameters.
In the NEPHRON+ project the development of a mobile dialysis device, aiming at home-based and continuous treatment, is augmented by the design of an integrated infrastructure for the treatment. [2] The system under development combines sensors integrated into the device with medical measurement devices for the observation of the patient's vital parameters. This system allows to propagate the crucial interacting parameters during the course of treatment.

2 Methods

In the development of a mobile dialysis system various means of monitoring were integrated to enable the supervision of crucial medical parameters as a basis for automated adaptation of the treatment. A use case defines the application of the system and allows for standardized measuring conditions. Image 1 shows an overview of the integrated sensing system.
Self-monitoring of the dialysis device is enabled through the integration of sensors. In addition to sensing of device-related parameters, like heat dissipation or pressure of the transported blood, ion selective and enzymatic sensors allow continuous measurement of changes of chemical concentrations and therefore the primary effect of blood cleansing. Another direct treatment effect is the removal of surplus fluid, which is assessed by a weight scale. Weight measurements are wirelessly transmitted through Bluetooth Health Device Profile to a transceiver in the dialysis device. To minimize disturbances in the estimation of the fluidic status the patient weighs himself directly after get-

ting up in the morning under standardized conditions. Additionally, a confirmation of the surplus of fluid to be removed is requested from the patient via a user interface.

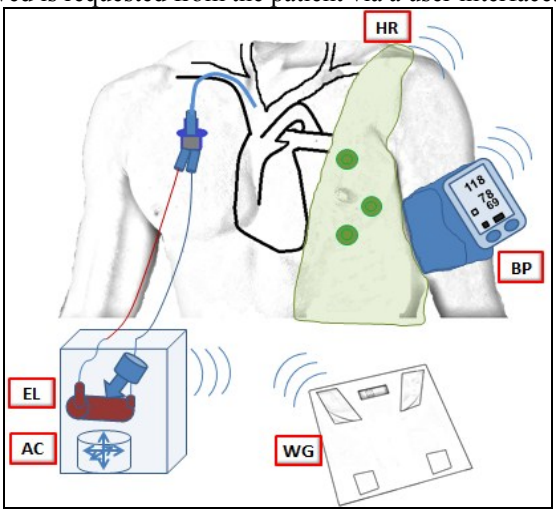

Image 1 Sensing System: EL) concentration electrodes, AC) acceleration sensors integrated | HR) heart, BP) blood pressure and WG) weight monitoring linked wirelessly.

Through the same interface also vital parameter measurements are transmitted from external sensing devices. An automatic sphygmomanometer is used to measure blood pressure several times a day. An unobtrusive electrocardiogram sensing device based on smart garment technology enables registration of heart rate and furthermore intermediately record episodes of ECG data. [3]
The system reminds the patient to use these devices at definable times.

3 Results

While the developed system measures physiological parameters, a diagnostic assessment needs to regard their mutual relations. Therefore at first instance models for the direct effect of blood cleansing treatment were taken into account. This model is complemented by the relationship with vital parameters and their interrelation with the chemical substances affected by the blood cleansing treatment.

3.1 Primary Effects of Blood Cleansing

The predominant model assumption for conventional dialysis therapy describes the physiology divided into compartment models. In this context, a compartment is a composition of tissues in the human body reacting similarly to the influence of the treatment. As the primary aim of dialysis is to affect chemical composition of the blood and fluidic balance of the patient, each compartment comprises a volume of fluid with distinct concentrations. Typically one or two compartments are regarded to be adequate to describe the effects observed during dialysis treatments. In the case of a one-compartment model all fluid in the body is assumed to be a unified volume. The concentration within this volume is elevated by ingestion of a certain substance and lowered by the blood cleansing treatment. In the case of two-compartment models the body is divided into an intracellular and an extracellular compartment, which communicate via the cell membrane. Patients with end stage renal disease are not able anymore to get rid of (uremic) waste products and excess fluid. Therefore, fluidic volume and concentration of a substance are only lowered by the removal $\boldsymbol{R}$ as an effect of the treatment. In equation 1 the joint removal rate $\boldsymbol{R_j}$ comprises both, removal by adsorption and removal due to fluid extraction $\boldsymbol{R_j = R_{ad} + R_{fe}}$. The reciprocal effect is caused by ingestion $\boldsymbol{I}$ leading to concentration and fluidic gain.
Imbalance of concentrations is counteracted by permanent exchange processes between the compartments. Passive concentration-driven diffusion is characterized by specific diffusion constants determined by the permeability of the cell membranes. For some substances additional effects contribute to the balance between the compartments, such as active transport processes. This is particularly the case for the distribution of sodium and potassium. The sodium-potassium co-transporter establishes an active redistribution against concentration gradients, resulting in disequilibrium, which is essential for elementary physiological processes like excitation and neural activity.
Equation 1 formulates the basic differential equation to describe a two compartment system following [4]. It describes the dependence of intra- and extracellular molar mass ($\boldsymbol{dM_{ec}/dt}$ and $\boldsymbol{dM_{ic}/dt}$), of intra- and extracellular volumes ($\boldsymbol{V_{ic}}$ and $\boldsymbol{V_{ec}}$), diffusion coefficient ($\boldsymbol{D_c}$), active trans-cellular transport coefficient ($\boldsymbol{A_C}$), extracellular concentration for half-activation of active transport ($\boldsymbol{K_m}$), ingestion ($\boldsymbol{I}$) and removal ($\boldsymbol{R}$).

$$\frac{d\,M_{ec}}{dt} = D_c \cdot \left(\frac{M_{ic}}{V_{ic}} - \frac{M_{ec}}{V_{ec}}\right) - A_c \cdot \left(\frac{\frac{M_{ec}}{V_{ec}}}{\frac{M_{ec}}{V_{ec}} + K_m}\right) - R_j + I \qquad \frac{d\,M_{ic}}{dt} = A_c + D_c\left(\frac{M_{ec}}{V_{ec}} - \frac{M_{ic}}{V_{ic}}\right) \qquad \textbf{(1)}$$

From the compartment model equation (1) the models for the involved substances are derived, regarding contributing processes: In the distribution of potassium a two compartment model equivalent to (1) is appropriate, as it allows the description of a decrease during hemodialysis, as well as processes leading to increase of measured concentrations. [4]
Modelling urea distribution with two compartments was proven to be adequate, as well. As opposed to potassium, it is not influenced by active exchange processes. Therefore, the addend describing the active transport does not apply in this case, rather only passive exchange is assumed. [5], [6]
Sodium is contained predominantly in the extracellular compartment. Therefore, the effects typical for a two compartment distribution cannot be observed. [6], [7] This especially holds true for the effect referred to as rebound, which describes the rapid increase of concentrations in the extracellular compartment as reflected in plasma measurements – due to diffusion from the intracellular compartment following dialysis. The model according to [6] describes the distribution of sodium in combination with urea and additionally considers fluidic distribu-

tion. Since dialysis also aims at eliminating of excess fluid, it is mandatory to regard the distribution of fluid volume in the compartments $\mathbf{V_{ex}}$, $\mathbf{V_{in}}$ as well. This relation is described according to [6] in the following equation 2, considering the concentration gradient at the cell membrane.

$$V_{ex}(t) = V_{tot}(t)\left[1 + \frac{M_{u,in}(t) + M_{K,in}(t) + M_{eq,in}}{M_{Na,ex}(t) + M_{u,ex}(t) + M_{K,ex}(t) + M_{eq,in}}\right]^{-1} \qquad (2)$$
$$V_{in}(t) = V_{tot}(t) - V_{ex}(t)$$

Consequently, the fluid balance chains the compartment models of the different substances, resulting in a dependency between each other, as shown in Image 2.

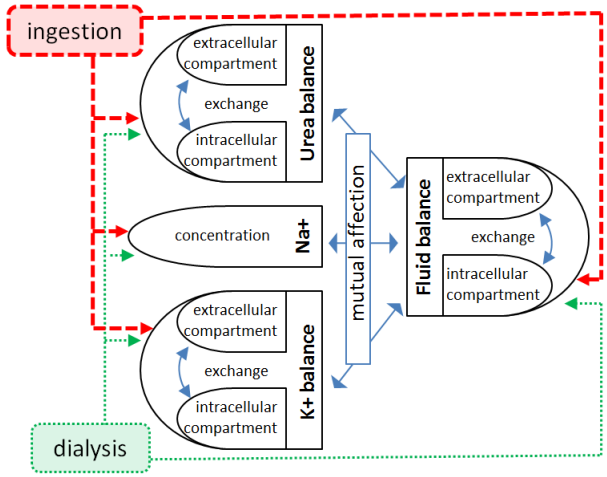

Image 2 Multi-compartment model describing sodium, potassium, urea and fluidic balance.

These model assumptions are the basis to describe the dynamic behaviour of the chemical composition of the blood. The profile of the substances is affected by exterior influences on the system: ingestion ***I*** by food intake and reduction ***R*** by the blood treatment. Both affect only the extracellular compartment directly. Therefore, blood cleansing therapy has direct effect on the extracellular compartment, while the intracellular one is only affected indirectly by the exchange processes.

3.1.1 Concentration Dynamics

The physiology of a patient can be modelled as a multi-compartment system with a foreseeable influence by blood cleansing. However, simply relying on this assumption would ignore the dynamic and time variant physiological behaviour of the fluidic and concentration distributions. During dialysis especially the intake of food is expected to result in temporal transient gradients of concentration. The physiological reactions to the ingestion of meals, particularly containing high concentrations of the regarded substances, have been studied. In healthy subjects such transient intakes of nourishment are not critical. Patients with end stage renal disease suffer from a dramatically reduced capability to compensate such intake. To account for the effects of nourishment the increase of fluid volume as well as substances need to be taken into account. Such reactions to ingestion were analysed for potassium [8] or urea [9], for instance.

3.2 Influence on Vital Signs

Vital sign monitoring is also an essential part of renal replacement treatments. [10] Homeostatic imbalance of electrolytes, influenced by hemodialysis, might lead to impairment of vital functions, as for instance ionic concentration shifts are the basic mechanism for cardiac excitation. The influence of chemical concentrations on vital signs cannot be defined straightforwardly, as there are additional influencing factors contributing to this development. However, a number of studies have investigated the influence on heart rate and blood pressure and even their dependence on the chemical concentrations which are targeted by dialysis.

3.2.1 Vital Sign Dynamics

Vital signs like heart rate and blood pressure are influenced by physical and mental activity, the behaviour of the patient or even environmental factors. Not all of these details can be accounted in the model concept. Rather it is sensible to observe the most important variables. Particularly an accelerometer is integrated in the developed system to monitor motions. Accordingly the so assessed physiological activity can be considered as a dominant influencing actor on the development of vital signs.
In the study by [11] an acceleration sensing device in the size of a wristwatch was applied in renal disease patients. Accelerations exceeding a predefined threshold were recorded and their sum over time slots regarded as an indicator for the level of activity. For this measurement a correlation was observed to the systolic and diastolic blood pressure as well as the heart rate. Based on the relations reported in this study, equations 3 were derived as estimation for the influence of the measured variable, referred to as activity count (AC), on the vital sign measurements.

$$BPdia\langle mmHg\rangle = 120 + \sqrt{AC}\cdot 1.36$$
$$BPsys\langle mmHg\rangle = 64 + \sqrt{AC}\cdot 1.07 \qquad (3)$$
$$HR\langle BPM\rangle = 70 + \sqrt{AC}\cdot 1.24$$
$$\text{with } \sqrt{AC} = [0..15]$$

This model provides an estimation of the vital parameters based on a given activity. In this context another study is of particular interest, which investigated the development of vital signs dependency on circadian rhythm and gives the opportunity to roughly estimate their development over a day. [12]

3.2.2 Chemical Concentrations Influence on Vital Signs

In addition to the predominant effect of activity on vital signs, various investigations unveiled, that changes in electrolyte levels, especially their deviation from standard physiological range, induce changes of blood pressure and heart rate.

3.2.2.1 Influence on Blood Pressure

Various studies have been conducted to investigate relations between sodium and potassium levels and their impact on blood pressure. Summarizingly a tendency for in-

creased blood pressure seems to originate from high sodium and low potassium levels. In contrast and opposed tendency for hypotension was not observed. [13], [14]
In addition the combined analysis of both substances shows an antagonizing effect of potassium on hypertension induced by high sodium supplementation. [15],[16]
No influence of urea on blood pressure has been reported, as even high direct administration did not lead to any changes. [17]

3.2.2.1 Influence on Heart Rate

Changes in serum potassium level, increases as well as decreases, could lead to alterations of the ECG waveform, while severe hyperkalaemia may even result in heart fibrillation. [18] However, changes in ECG signal do not always occur and especially hemodialysis patients not often develop any noticeable alterations. [19], [20]
These effects related to potassium and are not reported for other substances targeted by dialysis. [21]

4 Conclusion

The development of a system for mobile dialysis treatment includes the implementation of integrated multimodal sensing to monitor the patient and control the therapy. This creates the prerequisites for a safe and efficient dialysis treatment out of clinical settings and without the constant supervision of a medical professional. A system was realized considering a well-defined use case to enable monitoring of vital parameters. Experts' opinions for the technical realization and combined analysis of the parameters were supported by literature research which yielded the complex relations between the physiological parameters. The findings allow to analyse the various measurements in a context-aware manner. The system will serve as the basis for monitoring and adaptive control of a newly developed dialysis device to be put to the test in clinical trials. This will facilitate a home-based treatment with the potential to also support conventional hemodialysis.

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