A Physiological Closed Loop System to Prevent Intradialytic Hypotensive Episodes

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Abstract

Intradialytic hypotensive episodes are still the most frequent complications in dialysis treatments. One of the reasons that causes hypotensive episodes is the application of a non-adequate net fluid removal rate.

This work presents the development of a physiological closed loop system, which is applied during a dialysis treatment with the aim to prevent hypotensive episodes. This system is based on two physiological parameters that reflect a patient's cardiovascular condition: the systolic blood pressure and the relative blood volume. From the evaluation of these two parameters an adequate net fluid removal rate is calculated.

The physiological closed loop system is based on fuzzy logic and was developed modularly. It consists of one module each to monitor the short and long time trend of systolic blood pressure, and one module to monitor the relative blood volume. These modules evaluate the trend of their respective parameter and calculate a value that represents a patient's cardiovascular stability every five minutes. These three values are weighted and combined into a single value representing a patient's momentary cardiovascular stability. Based on this value and the withdrawn net fluid removal volume, the system calculates an adequate net fluid removal rate that is then applied to the patient for the next five minutes.

The physiological closed loop system was verified and validated using the knowledge of medical experts, a laboratory test setup and a clinical pilot study. All three evaluation methods showed that the closed loop system is able to stabilise a patient's cardiovascular condition, and therefore to prevent and reduce hypotensive episodes. The pilot study comprised 106 treatments on six patients and showed that 83 % of all patients had higher cardiovascular stability when using the developed physiological closed loop system than when using a constant net fluid removal rate.

A product based on the physiological closed loop system is currently under development and will be incorporated into dialysis machines.

Zusammenfassung

Intradialytische hypotensive Episoden bleiben weiterhin die häufigsten Komplikationen aller Dialysetherapien. Die Ursachen von hypotensiven Episoden sind multifaktoriell. Dazu gehört unter anderem das Applizieren einer nicht adäquaten Ultrafiltrationsrate.

Im Rahmen dieser Arbeit wurde ein für Dialysetherapien bestimmter physiologischer Relgelkreis entwickelt, der hypotensive Episoden reduziert beziehungsweise verhindert. Der Regelkreis regelt zwei physiologische Parameter, die den physiologischen Zustand des Patienten während einer Dialysetherapie widerspiegeln. Diese zwei physiologische Parameter sind der systoliche Blutdruck und das relative Blutvolumen. Der Regelkreis evaluiert diese Parameter und stellt eine adäquate Ultrafiltrationsrate ein.

Der physiologische Regelkreis basiert auf einer Fuzzy Logik und wurde modular entwickelt. Der Regelkreis enthält je ein Modul zur Überwachung des Kurzzeit- und Langzeittrends des systolischen Blutdruckes, und zusätzlich noch ein Modul zur Überwachung der Veränderung des relativen Blutvolumens. Diese Module überwachen den Trend ihrer entsprechenden Parameter und berechnen alle fünf Minuten je eine Variable, die den aktuellen kardiovaskulären Zustand des Patienten widerspiegelt. Die drei berechneten Variablen werden in einer Gewichtungseinheit gewichtet und zu einem Wert kombiniert, der den aktuellen kardiovaskulären Zustand des Patienten wiedergibt. Diese kombinierte Variable wird mit dem zum aktuellen Zeitpunkt der Therapie entzogenen Ultrafiltrationsvolumen abgeglichen und für die Berechnung der Ultrafiltrationsrate für die nächsten fünf Minuten angewendet.

Der physiologische Regelkreis wurde mit Hilfe von medizinischen Experten, eines Laboraufbaus und einer Pilot-Studie verifiziert und validiert. Die aus 6 Patienten und 106 Therapien bestehende Pilotstudie zeigte, dass 83% aller Dialysepatienten einen besseren kardiovaskulären Zustand erreichten, wenn sie mit dem entwickelten physiologischen Regelkreis behandelt wurden, verglichen mit einer konstanten Ultrafiltrationsrate.

Ein auf dem physiologischen Regelkreis basiertes Produkt ist derzeit in Entwicklung und wird in Dialysemaschinen implementiert.

Contents

Chapter 1

Introduction

Intradialytic Hypotensive Episodes (HEs) are still 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%) [15, 115]. HEs do not only increase morbidity and reduce quality of life of patients with chronic kidney disease [16], but are even an independent risk factor for mortality [95, 104].

An HE is a reduction in *Blood Pressure (BP)* [1] associated with symptoms [41, 44]. The *Kidney Disease Outcomes Quality Initiative (KDOQI)* [41] defines an HE as a decrease in systolic *BP* greater than $20\,mmHg$ or a decrease in *Mean Arterial Pressure (MAP)* 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 [51, 59].

Hypovolemia is the main initiator of HE [3, 11, 114]. It is a consequence of too high a rate of water removal during the dialysis treatment [82]. 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 of biofeedback systems that aim to reduce hemodynamic instability and prevent HE. These techniques monitor dialysis-related physiological and hemodynamic parameters (e.g. *Hematocrit (HCT)*, blood temperature, blood pressure) to adjust machine-related parameters (e.g. *Net Fluid Removal (nfr)*-rate, dialysate conductivity) [16, 17, 79].

[1] BP: we will use the abbreviation BP in this thesis to denote systolic blood pressure.

It has been demonstrated that biofeedback systems that monitor a single physiological parameter increase quality of life and reduce HEs [51, 56, 59, 89]. However, these biofeedback systems reduce HEs by only 25 % - 39 % [51, 59, 81].

The main purpose of this thesis is to develop a biofeedback system that monitors two physiological parameters, *BP* and *Relative Blood Volume (RBV)*, and adjusts the nfr-rate based on a combination of their properties. In this way, we aim to reduce interventions of medical staff, to reduce dialysis related complications such as HEs, and most importantly to provide a better quality of life to the patient.

This thesis begins with an overview of the background information needed to understand our work in Chapter 2. In particular, we explain the functionality of a hemodialysis treatment and the pathogenesis of HEs. This chapter also introduces the state of the art with respect to techniques aimed to prevent HEs.

Chapter 3 presents the development of the biofeedback System BioLogic Fusion, beginning with a motivation for this development. The architecture of BioLogic Fusion is presented. The development of the fuzzy systems that constitute BioLogic Fusion is then described.

Chapter 4 reports the verification and validation of both BioLogic Fusion and the fuzzy systems of which BioLogic Fusion consists. First, verification and validation by applying existing treatment data to these systems are demonstrated. Second, a validation of BioLogic Fusion in the laboratory with the help of a test setup that simulates a cardiovascular circuit is presented. Third, a validation of BioLogic Fusion in a pilot study is described.

In chapter 5, we discuss the development of BioLogic Fusion taking into consideration the benefits and limitations of the developed fuzzy modules. In addition, the results of each of the presented validation methods is put into context and an outlook regarding biofeedback systems in dialysis is discussed. Finally a paragraph concludes our work.

Chapter 2

Background

1 Kidney and Hemodialysis

1.1 Renal function and failure

The kidney is one of the most important organs in the human body. It has three main functions: First, excretion function. This comprises, for example, excretion of metabolic waste products, foreign chemicals and drugs. Second, regulation function, which incorporates regulation of water and electrolytes balance and concentrations, body fluid osmolality, arterial pressure and acid-base balance. Third, genesis function, for example, gluconeogenesis, genesis of renin and erythropoietin.

If the kidneys fail to fulfill their functions, e.g. because of diabetes or hypertension, two alternatives are available to replace this failure: First, kidney transplantation and second, extracorporeal blood treatment. To date, 93.000 people are waiting for kidney transplantation [43]. Until a donor kidney becomes available, their failed kidney function is replaced by extracorporeal blood treatment such as hemodialysis.

1.2 Hemodialysis

Hemodialysis is an extracorporeal blood treatment and is the most common method to treat kidney failure. Hemodialysis has two main goals: Removing uremic toxins and excess water from the patient's body.

Figure 2.1 depicts the principle of a hemodialysis. An arterial and a venous needle are inserted into the arterio-venous fistula of the patient. Via the arterial needle,

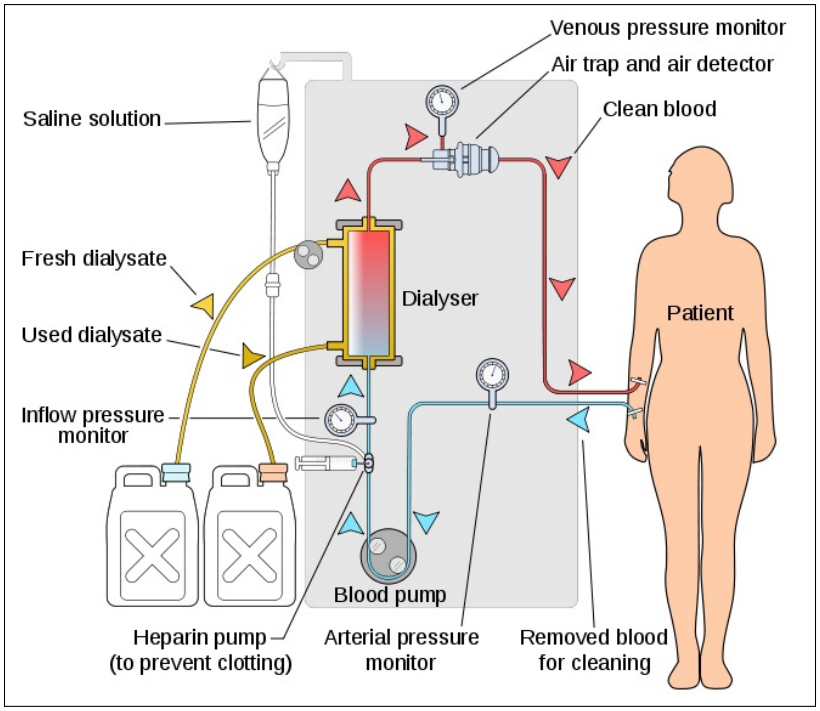

Figure 2.1: Blood side of a hemodialysis treatment. From the arterial needle, blood is pumped to the dialyser, where it is purified. From the dialyser, blood is directed to a venous bubble catcher and then back to the intracorporeal circulation [21].

blood is pumped with a blood pump through the arterial blood line system to the dialyser. In the dialyser, blood is purified and returned back to the patient by the venous blood system.

In the dialyser, the blood is brought into contact with the so-called dialysis water[1], separated only by a semipermeable membrane. Dialysis water and blood flow are in opposite directions (counter current flow). This maintains the concentration gradient across the membrane at a maximum and increase the efficiency of the dialysis. The transport mechanisms in the dialyser, with which uremic toxins and excess water are removed from the blood, are diffusion, ultrafiltration, osmosis and convection.

This work focuses on the ultrafiltration, which withdraws water from the patient. The volume of withdrawn water is called net fluid removal volume (nfr-volume). The rate, with which water is withdrawn is called net fluid removal rate (nfr-rate).

[1]Dialysis water: an electrolyte solution, which is provided by the dialysis machine.

2 Genesis of Intradialytic Hypotensive Episodes

To date, the genesis of HEs has not been completely understood. Its etiology is multifactorial [66]. However, nephrologists agree that three main factors contribute to the genesis of HEs: Preservation of blood volume, systemic vascular resistance and cardiac output [14, 38].

Preservation of blood volume

The fluid removal during dialysis decreases vascular hydrostatic pressure and increases colloid osmotic pressure. This results in a shift of water from the extravascular to the intravascular compartment, the so-called refill [36, 70, 91]. However, if the nfr-rate is larger than the refilling-rate over a sustained amount of time, hypovolemia occurs, resulting in HE [6, 77].

Dialysate sodium concentration is a further parameter that influences the preservation of blood volume. Higher dialysate than plasma sodium concentration at the beginning of the dialysis treatment prevents the decrease in plasma osmolality [24, 61, 63]. Lower dialysate than plasma sodium concentration at the end of the treatment prevents sodium accumulation. Both techniques allow water shift from the intracellular to the intravascular compartment to preserve blood volume. However, it is important to note that higher post- than pre-dialysis sodium concentration may result in water intake and may lead to hypervolemia and thus hypertension [2].

Hypertension itself may influence blood volume preservation. Due to venous compliance in such hypertensive patients, the postcapillary pressure in the venules is higher than in normotensive patients for a given level of blood volume, reducing water to shift from the interstitial to the vascular space [52].

Acetate as dialysate buffer also influences blood volume preservation. It induces arteriole vasodilation that increases precapillary hydrostatic pressure, inducing water shift from the intravascular to the extravascular space [38].

Another contributing factor that influences blood volume preservation is intradialytic food intake. This contributes to a redistribution of the blood from the large vessels to the splanchnic organs, which may cause hypovolemia and thus HE [8, 94].

Systemic vascular resistance

Water removal during hemodialysis also results in venous constriction, contributed by the efferent sympathetic pathways (part of the autonomous nervous system). Venous vasoconstriction increases venous capacity to maintain BP. These pathways still function in non-diabetic patients. Nonetheless, these patients are still prone

to HEs [38]. This means that the vascular response in these patients is caused by the dialysis treatment itself. During hemodialysis, absolute blood volume in the central vascular system is preserved by reducing blood flow to the periphery (skin and muscles) [38]. Consequently heat exchange over the periphery is reduced and the body temperature increases. If the patient cannot tolerate the rise in core body temperature, a vasodilation of the peripheral vascular system occurs [33]. However, the blood volume in the peripheral vascular system remains unchanged, which leads to an HE.

Cardiac output

Cardiac output is a major factor in maintaining hemodynamic stability. It is the ratio of the arterial pressure and the total peripheral resistance [33]. Cardiac output depends on cardiac filling volume, cardiac contractility and heart rate. Compliance of the venous system, in which the backflow of stressed blood (peripheral venous blood) to the heart takes place, has major importance in maintaining cardiac filling volume, and thus cardiac output. When venous compliance is reduced in dialysis patients, a small increase in blood volume (e.g. caused by refill) results in a rapid rise in venous pressure. Conversely, a small decrease in blood volume (e.g. caused by nfr) causes a steep decline in venous pressure.

Hypovolemia may also mobilise the hemodynamically unstressed blood volume (splanchnic venous blood) to the stressed compartments by vasoconstriction, influencing venous return and thus cardiac output.

A further hemodynamic response to hypovolemia is the diastolic function of the heart. Changes in blood volume increase the sensitivity (response) of the cardiac output of the heart. Thus, a small decrease in ventricular volume results in a steep decrease in left ventricular pressure. In addition, this decrease in ventricular volume stimulates the left ventricular baroreceptors that activate the sympatico-inhibitory cardiopressor reflex - the Bezold-Jarisch-reflex, which decreases the heart rate, leads to vasodilation, inducing HE. [38]

3 Preventing Hypotensive Episodes

3.1 Clinical routine methods

Conventional methods that aim to prevent HEs are established in clinical practice. They are summarized here: