Initial Systolic Time Interval (ISTI) as a Predictor of Intradialytic Hypotension (IDH)

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Abstract. In haemodialysis treatment the clearance and volume control by the kidneys of a patient are partially replaced by intermittent haemodialysis. Because this artificial process is performed on a limited time scale, unphysiological imbalances in the fluid compartments of the body occur, that can lead to intradialytic hypotensions (IDH). An IDH endangers the efficacy of the haemodialysis session and is associated with dismal clinical endpoints, including mortality. A diagnostic method that predicts the occurrence of these drops in blood pressure could facilitate timely measures for the prevention of IDH. The present study investigates whether the Initial Systolic Time Interval (ISTI) can provide such a diagnostic method. The ISTI is defined as the time difference between the R-peak in the electrocardiogram (ECG) and the C-wave in the impedance cardiogram (ICG) and is considered to be a non-invasive assessment of the time delay between the electrical and mechanical activity of the heart. This time delay has previously been found to depend on autonomic nervous function as well as preload of the heart. Therefore, it can be expected that ISTI may predict an imminent IDH caused by a low circulating blood volume. This ongoing observational clinical study investigates the relationship between changes in ISTI and subsequent drops in blood pressure during haemodialysis. A registration of a complicated dialysis showed a significant correlation between a drop in blood pressure, a decrease in relative blood volume and a substantial increase in ISTI. An uncomplicated dialysis, in which also a considerable amount of fluid was removed, showed no correlations. Both, blood pressure and ISTI remained stable. In conclusion, the preliminary results of the present study show a substantial response of ISTI to haemodynamic instability, indicating an application in optimization and individualisation of the dialysis process.

1. Introduction
Haemodialysis (HD) is a therapy that supports or replaces kidney function in the case of renal failure. Although haemodialysis is a life saving therapy for end-stage renal patients it entails various side effects [1], and the patient population shows a high morbidity rate [2]. Especially intradialytic hypotension (IDH) is a persistent problem for about 20-25% of the HD patients. IDH is defined as an abrupt (over 10 to 15 min) decrement in blood pressure accompanied by symptoms such as: abdominal discomfort, yawning, nausea, vomiting, muscle cramps, dizziness, fainting, or a decline of blood pressure requiring a nursing intervention [3].
IDH originates primarily from a decrease in blood volume due to fluid removal by HD and a delayed refill of fluid from other parts of the body. The body can be considered to consist of three compartments that contain fluid: the intravascular compartment containing blood, the interstitial space surrounding cells and the intracellular space inside cells (see figure 1). Fluid removed by HD is withdrawn from the intravascular compartment which should be complemented by fluid from the interstitial and the intracellular space. However, in some circumstances this process is not fast enough, or is counteracted by osmotic fluid transport from the hypotonic blood compartment to the hypertonic interstitial and intracellular space, which can result in an IDH.

The use of impedance cardiography (ICG) to study haemodynamic stability has been reported before by Meijer et al. in patients, admitted to the intensive care unit after cardiac surgery [4]. In these patients, fluid was administered intravenously in order to expand the circulating volume of the intravascular compartment. This situation can be viewed as a mirror image of haemodialysis. Meijer et al. showed that an interesting aspect of the ICG-signal can be found in the time-relationships, when the moments of occurrence of specific waves in the ICG are compared to specific points in the electrocardiogram (ECG) [5]. They introduced the Initial Systolic Time Interval (ISTI), where the ISTI was defined as the time interval between the R-point in the ECG and the C-point in the ICG (see figure 2).

Assuming that ISTI depends on preload of the heart by way of the Frank-Starling mechanism and on autonomic nervous control of the heart, it can be expected that ISTI is influenced by an imminent IDH during haemodialysis and that ISTI may be used as a predictor of IDH. Moreover, previous research showed an inverse relationship between ISTI and cardiac output [4] and a decrease of ISTI during a Valsalva manoeuvre [6]. The present study investigates whether ISTI can be used to evaluate and predict hypotensive periods during dialysis, and the present paper reports on preliminary results obtained from patients undergoing haemodialysis.

2. Method
ICG recordings were made using a four-electrode system attached to the left side of the body described in detail by Meijer et al. [5]. The outer two electrodes applied a small alternating (64 kHz) electrical current $i$ of $0.3 \text{ mA (r.m.s.)}$ through the upper part of the body. The inner two electrodes continuously measured the subsequent electrical voltage difference $V(t)$ over the region of the heart,
from which the electrical impedance $Z(t)$ was computed continuously. The ECG signal was derived simultaneously from the two inner electrodes. Recordings were made using an impedance cardiograph designed and built at the Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, the Netherlands. The signals were AD-converted using an ADInstruments PowerLab 8SP and processed on a personal computer using ADInstruments Chart (version 5.1.1) for Windows.

The study was performed on the Nephrology department of the VU University Medical Center. Continuous registrations of ECG and ICG were made during standard dialysis sessions. Also blood pressure (BP) and the relative blood volume (RBV) were registered by the dialysis machine (Nikkiso DBB-07). Recordings of 1 minute with a time interval of 15 minutes of these parameters were made in a resting state (lying or sitting) and processed. All patients gave their written informed consent prior to participation in the study.

3. Preliminary results

Figure 3 shows examples of a complicated dialysis (A) and one of an uncomplicated dialysis (B).

![Figure 3](image_url)

**Figure 3.** Two typical examples of a complicated dialysis (A) and an uncomplicated dialysis (B). The top graph shows both the systolic (red) and diastolic (blue) blood pressure. The middle graph shows the relative blood volume as a percentage of the initial blood volume (left) and the ultrafiltration rate (right). The bottom graph shows the mean ISTI ± SD (left) and the RR-interval of the ECG (right).

The registration of the complicated dialysis was taken from a 61-years old woman (162 cm, 90 kg), during a normal haemodialysis session of 4 hours. Due to dizziness, the session was limited to 3.45 hours in which 3510 ml of fluid was extracted by ultrafiltration. In order to prevent a severe hypotension the ultrafiltration rate was adjusted after 120 minutes of haemodialysis. During this dialysis session, the systolic blood pressure (SBP) decreased from 149 mmHg at the start to 72 mmHg at the end. Parallel, ISTI showed an increase from 149 ms to 186 ms. Regression analysis showed a strong significant correlation between ISTI and SBP ($p < 0.005$) and between ISTI and RBV ($p < 0.001$), shown in respectively figure 4 and 5.
A registration of an uncomplicated dialysis is shown in figure 3B. This registration was taken from a 50-years old male (176 cm, 105 kg) during a normal dialysis session of 4 hours in which 3100 ml of fluid was extracted. During this uncomplicated dialysis session SBP remained stable at 95 mmHg while the ultrafiltration rate was high and RBV decreased. ISTI and RR also remained stable. Regression analysis showed no significant correlation between ISTI and SBP (p > 0.05) and between ISTI and RBV (p > 0.05).

**Figure 4.** Relationship between ISTI and systolic blood pressure (SBP) during the complicated dialysis session (r = 0.736, p < 0.005). Data are means ± SD.

**Figure 5.** Relationship between ISTI and relative blood volume (RBV) during the complicated dialysis session (r = 0.887, p < 0.001). Data are means ± SD.

4. Discussion and conclusion
The present study focuses on the evaluation of the use of ISTI to predict IDHs. So far, not sufficient registrations of an IDH were made to draw decisive conclusions. The preliminary results are consistent with the expectation that in the case of an IDH the ISTI increases and in the case of an uncomplicated dialysis the ISTI remains stable. The major difference between the two examples is that during the complicated dialysis session an IDH occurs and during the uncomplicated session not, while a similar amount of fluid was removed. Although the cause of an IDH is not fully understood, the extraction rate of fluid from the intravascular compartment in relation to the refill by fluid from the other body compartments is of importance. Further, the degree of overfilling may play an important role. An overfilled patient has a stable, high preload and an operating point of the heart on the upper part of the Frank-Starling curve. Because ISTI depends on the preload of the heart, ISTI is expected not to change in an overfilled person during haemodialysis, which is consistent with the observations.

In conclusion, the preliminary results of the present study show a substantial response of ISTI to haemodynamic instability, indicating an application in optimization and individualisation of the dialysis process.

References
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