Pilot study to detect changes in blood flow in the external auditory meatus during haemodialysis

Suree Yoowannakul[1] MD, Terence S. Leung[2] PhD, Andrew Davenport[1] FRCP

[1]UCL Centre for Nephrology, Royal Free Hospital, London
[2]Department of Medical Physics and Biomedical Engineering, University College London, London

Suree Yoowannakul, moo_yookul@hotmail.com, Terence Leung , t.leung@ucl.ac.uk
Andrew Davenport, andrewdavenport@nhs.net

Address for correspondence
contact andrewdavenport@nhs.net
UCL Department of Nephrology, Royal Free Hospital, University College London, Rowland Hill Street, London NW3 2PF
tel 44-2074726457
fax 44-2073178591

short title blood flow external auditory meatus

key words hypotension extracellular water blood flow bioimpedance haemodialysis pulse amplitude
the authors have no conflicts of interest

Acknowledgements: Dr Suree Yoowannakul was in receipt of International Society of Nephrology and Kidney Research UK training award

Abstract
Background

Blood flow to internal organs is reported to fall during haemodialysis (HD). As such, there non-invasive monitoring devices are required to detect changes in perfusion, which could then be used for therapeutic interventions. We report on a pilot study monitoring blood flow in the outer auditory meatus.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/tap.13433

Methods

We measured the maximum pulse wave amplitude and indicators of blood flow by analysing red and green colour changes in the outer auditory meatus from video recordings made using an otoscope fitted with a digital camera during haemodialysis treatments.

Results

We studied 61 patients, 43 (71.5%) male, mean age 64.9 ± 12.7 years. Weight fell from 72.8±22.5 pre-dialysis to 71.5±22.1 kg post-dialysis ($p<0.001$). Blood pressure did not significantly change (pre-dialysis 142±29/ 67±18 to 143±25/68±17 mmHg post-dialysis). The maximum pulse wave amplitude in the external auditory meatus fell from 0.21 (0.1-0.55) to 0.14 (0.04-0.4) after 90 minutes, $p<0.001$, and remained low thereafter, and the change at the end of the dialysis session was associated with percentage weight loss ($r= -0.37$, $p=0.003$). Green and red pixel values did not change (pre-dialysis 0.339 (0.333-0.345) to 0.302 (0.291-0.33) post, and 0.301 (0.293-0.328) pre-dialysis to 0.339 (0.334-0.347), respectively).

Conclusion

This pilot study showed that the maximum pulse wave amplitude measured in the external auditory meatus fell during the dialysis session, and that the fall was associated with fluid removal. This could potentially lead to the development of a monitoring device which could fit in the ear and record during the dialysis session.

Introduction

World-wide, haemodialysis is the most common treatment for patients with chronic kidney disease stage 5 (CKD5d), with almost two million patients now receiving treatment. Despite the wide-spread availability of haemodialysis, complications may occur during treatments [1]. As fluid is removed from the patient during most treatments, symptomatic hypotensive episodes and a fall in systolic blood pressure remain the most complications [2]. Patients who have repeated episodes of intra-dialytic hypotension are at greater risk of

mortality [3,4]. However symptomatic hypotension appears to be the tip of an iceberg, as many more patients suffer a fall in blood pressure during dialysis without reporting any over symptoms [3]. More recently, studies have shown a reduction in perfusion to the heart and brain during haemodialysis unrelated to falls in blood pressure [5,6]. These repetitive episodes of reduced organ perfusion have been associated with permanent structural and functional damage [7,8] and increase the risk of patient mortality [9].

Over recent years several technological developments have been introduced including relative blood volume (RBV) monitoring, measuring changes in whole blood viscosity or haematocrit as blood passes from the patient into the haemodialysis circuit, by ultrasound or optical density methods [10]. Unfortunately, neither observational and prospective trials of this technology failed to demonstrate a reduction in hypotensive episodes [11-13]. Although refining the technology by introducing positive feedback loops to automatically respond to changes in the RBV slope reduced the number of asymptomatic and symptomatic hypotensive episodes [14].

As such, alternative methods are required to monitor changes in blood flow to organs during dialysis sessions to prevent organ ischaemia. Ideally these should be non-invasive, acceptable to patients and of low cost. Traditionally core body temperature has been measured by recording the sub-lingual, external auditory canal and rectal temperature. We therefore wished to explore whether we could detect changes in perfusion in the external auditory canal during haemodialysis sessions, as wearing a “hearing aid like device” could be an acceptable form of non-invasive monitoring during dialysis.

Methods

We studied blood flow in the external auditory meatus and the finger-tip in 61 adult haemodialysis patients, using the SuperEyes otoscope (1600X Digital Microscope USB Endoscope Camera, Shenzhen SuperEyes Tech Co. Ltd, Shenzhen China). Video recordings of

thirty seconds were made of the outer ear canal at the start, and then every 30 minutes during the haemodialysis session and then at the end of the session. Recordings were analysed (i) for the maximum amplitude of the arterial pulse derived by Fourier transforming the green pixel values and identifying the spectral peak matching the heart rate and (ii) to estimate tissue perfusion by measuring both red and green pixel values, as greater tissue perfusion or haemoglobin concentration would lead to a greater red pixel value (or greater reflected red light), and conversely a lower green pixel value (or lower reflected green light) as green light is absorbed by haemoglobin.

Patients were dialysed with Fresenius 5008H dialysis machines (Fresenius Medical Company, Bad Homburg, Germany) using polysulphone dialyzers (FX series, Fresenius, Bad Homberg, Germany) [15], and cooled dialysate at 35^{o}C. Blood pressure was recorded by integrated blood pressure module every 30 minutes, and at the end of the dialysis session along with relative blood volume. Patients were reviewed and dialysis prescriptions ordered by the clinical care team. Extracellular water (ECW) and intracellular water (ICW) volumes were measured at the start and end of dialysis (S10, InBody, Seoul, South Korea) [16].

Blood tests were taken concurrently pre-dialysis and analysed by standard methods for urea, creatinine, albumin, haemoglobin (Roche Cobas 400, Roche Diagnostics, Sysmex, Milton Keynes UK), and NT-proBNP (Roche Diagnostics, Burgess Hill, UK) [17,18].

Ethics

Patients provided informed written consent in keeping with the Helsinki accord. Ethical approval was provided by the United Kingdom National Research Ethics committee (15NW/0437).

Statistical analysis

Data is presented as mean ± standard deviation, median (interquartile range), or as percentage. We used the D'Agostino & Pearson normality test, and depending upon data normality, univariate correlation was performed using Spearman analysis. We used student's t test and Wilcoxon rank sum pair test for pre- and post-dialysis data, and the Kruskal Wallis test to analyse repeated data during the dialysis session, with appropriate post hoc correction using the Games-Howell test. Statistical analysis used Prism 8.1 (Graph Pad, San Diego, USA) and Statistical Package for Social Science version 24.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken as $p<0.05$.

Results

We studied blood flow in the ear and finger in 61 haemodialysis patients, 43 (71.5%) male, mean age 64.9 ± 12.7 years. median duration of dialysis treatment 29.0 (12.0-65.4) months, during their scheduled dialysis session. Twenty-two (36.1%) had diabetic nephropathy, 15 (24.6%) glomerulonephritis or vasculitis, 12 (19.7%) tubular-interstitial nephropathy, 6 (9.8%) hypertensive nephropathy and 6 (9.8%) unknown aetiology. Thirty-two patients (52.5%) were prescribed anti-hypertensive medications, median number of anti-hypertensive medications 1 (0-1). Nineteen patients (31.5%) had a past medical history of myocardial infraction, coronary artery stenting or by-pass surgery,10 (16.4%) aortic aneurysm, reno-vascular or peripheral vascular disease, and 4 (6.6%) history of cerebrovascular disease or transient ischaemic attack.

Video frames from the image captured by the digital otoscope were analysed both for red and green colour and the amplitude of the arterial pulse (Figure 1). Compared to the arterial pulse measured at the brachial artery, we were able to measure the arterial pulse more reliably in the external auditory meatus compared to the finger-tip, although there was no difference in the number of successful recordings when the systolic blood pressure was < 100 mmHg (Figure 2).

Weight fell from 72.8±22.5 pre-dialysis to 71.5±22.1 kg post-dialysis (p<0.001), with a reduction in relative blood volume from 100% to 90.6 ±6.2%, and with a dialysis machine ultrafiltration volume of 1.7 (1.24-2.18) litres. Blood pressure was 142±29/ 67±18 mmHg at the start of dialysis and 143±25/68±17 mmHg at the end of the dialysis session. No patient suffered symptomatic intradialytic hypotension. Pre-dialysis haemoglobin was 98.0 ±13.5 g/L, serum urea 17.4 ±7.0 mmol/L, creatinine 636 (490-821) umol/L, albumin 32.5 ±7.6 g/L. There was a correlation between haemoglobin and both red colour pixel values (r=0.253, p=0.049) and green colour pixel values (r=-0.282, p=0.028) recorded from the external auditory meatus at the start of the dialysis session. The maximum pulse wave amplitude in the external auditory meatus fell from 0.21 (0.1-0.55) pre to 0.08 (0.05-0.18) post dialysis (p<0.01), green colour pixel values pre-dialysis 0.339 (0.333-0.345) to 0.302 (0.291-0.33) post, and red colour pixel values 0.301 (0.293-0.328) pre-dialysis to 0.339 (0.334-0.347) post. ECW was 15.9±3.9 L pre and 16.0±3.7 L post dialysis and ICW 22.2±5.3 L pre and 23.3±5.1 L post-dialysis.

We then compared the relative change in blood pressure to the change in pulse wave amplitude and colour in the external auditory meatus, and only the pulse amplitude fell during the dialysis session (table 1).

At the end of the dialysis session there was a correlation between systolic blood pressure (SBP) and ECW (r=0.34, p=0.007) and ICW (r=0.34, p=0.008). There were correlations between the external auditory meatus maximum pulse amplitude and red colour pixel values (r=0.36, p=0.05), and negative associations with both green colour pixel values (r= -0.34, p=0.007) and heart rate (r=-033, p=0.009). In addition, there was a fall in green colour pixel values with increasing weight loss with (Figure 4), percentage weight loss (r= -0.37, p=0.003), and percentage ultrafiltration (r= -0.34, p=0.008).

Comparing the change in relative blood volume (RBV) monitoring at the end of the dialysis session we found an association with absolute weight change (r=-0.267, p=0.045),

percentage weight change (r=-0.354, p=0.01), and percentage ultrafiltration (r=-0.458, p<0.001).

Discussion

Despite advances in dialysis technology [19], the blood supply to the skin and other organs falls during a dialysis session [2,5,9]. Thus, studies which have used non-invasive monitoring with sensors placed on the forehead, fingers or toes have shown that this approach may have technical difficulties, unable to obtain reliable recordings, and as such have failed to show any relationship between changes in skin perfusion with changes in blood pressure during dialysis [20,21]. In keeping with these earlier studies, we were unable to a capture a significant number of pulse amplitude waveforms from the finger-tip. Core body temperature has been traditionally measured by placing a thermometer under the tongue, in the rectum and in the external auditory canal. After discussion with patient groups we chose to examine changes in blood flow in the external auditory meatus, as patients could potentially wear a device to monitor blood flow, similar to a hearing aid, throughout the dialysis session.

We found measuring changes in blood flow in the external auditory meatus more reliable than at the finger-tip. We observed an association between perfusion in the external auditory meatus as measured by green colour pixel values and haemoglobin concentration at the start of dialysis. During dialysis the amplitude of the arterial pulse wave in the external auditory meatus decreased as fluid was removed. Although intra-dialytic hypotension is a recognised complication of dialysis sessions, our patients did not have symptomatic hypotension, Indeed, our patient cohort was very stable as we did not observe a significant difference in SBP, DBP or pulse pressure. As such we could not analyse changes in perfusion in the external auditory meatus and changes in blood pressure. Although in keeping with recent studies reporting a reduction in cardiac, brain and other organ perfusion [5,6,9] we

noted a reduction in arterial pulse wave amplitude in the external auditory meatus during dialysis

We also used RBV monitoring, which was introduced some years ago as a technology designed to monitor vascular volume during dialysis. We found similar changes between the change in RBV at the end of the dialysis session and those of the maximum pulse wave amplitude measured in the external auditory meatus, in terms of change in weight, and ultrafiltration volume. Reports of RBV have shown a difference between the change in estimated intravascular volume and measurements of ECW and ICW [22]. In keeping with this earlier study, we found no association between changes in RBV and ECW or ICW at the end of the dialysis session.

Although fluid is removed during most haemodialysis sessions, the relationship between fluid removal and changes in ECW volumes and blood pressure are somewhat complex [23,24], and many patients suffer symptoms without marked changes in blood pressure and vice-versa [5]. As such, there is a requirement to monitor patient responses to haemodialysis, and ideally this should be non-invasive and allow continuous monitoring during the dialysis session. Our pilot study monitoring blood flow in the auditory meatus demonstrates that the arterial pulse amplitude falls with weight loss. This could potentially lead to the development of a monitoring device which could fit in the ear and record changes in perfusion during the dialysis session.

Acknowledgements

Dr Suree Yoowannakul was in receipt of International Society of Nephrology and Kidney Research UK training award

Disclosure

The authors have no conflict of interest. The results presented in this paper have not been published previously in whole or part

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee at which the studies were conducted (IRB approval number 15NW/0437) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Davenport A. Intradialytic complications during haemodialysis. Haemodial Int. 2006; 10(2):162-7
2. Kooman JP, Katzarski K, van der Sande FM, Leunissen KM, Kotanko P. Haemodialysis: A model for extreme physiology in a vulnerable patient population. Semin Dial. 2018;31(5):500-506
3. Reeves PB, Mc Causland FR. Mechanisms, Clinical Implications, and Treatment of Intradialytic Hypotension. Clin J Am Soc Nephrol. 2018;13(8):1297-1303
4. Yu J, Liu Z, Shen B, Teng J, Zou J, Ding X. Intradialytic Hypotension as an Independent Risk Factor for Long-Term Mortality in Maintaining Hemodialysis Patients: A 5-Year Follow-Up Cohort Study. Blood Purif. 2018;45(4):320-326
5. Meredith DJ, Pugh CW, Sutherland S, Tarassenko L, Birks J. The relationship between symptoms and blood pressure during maintenance haemodialysis. Hemodial Int. 2015;19(4):543-52
6. Buchanan C, Mohammed A, Cox E, Köhler K, Canaud B, Taal MW, Selby NM, Francis S, McIntyre CW. Intradialytic Cardiac Magnetic Resonance Imaging to Assess Cardiovascular Responses in a Short-Term Trial of Hemodiafiltration and Hemodialysis. J Am Soc Nephrol. 2017;28(4):1269-1277
7. Davenport A, Buscombe JR. Watershed cerebral infarction in a hemodialysis patient. Kidney Int. 2010;77(12):1140
8. Griva K, Thompson D, Jayasena D, Davenport A, Harrison M, Newman SP. Cognitive functioning pre- to post-kidney transplantation--a prospective study. Nephrol Dial Transplant. 2006;21(11):3275-82
9. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009;4(12):1925-31
10. Davenport A. Can advances in haemodialysis machine technology prevent intradialytic hypotension? Semin Dial. 2009;22(3):231-6
11. Booth J, Pinney J, Davenport A. Do changes in relative blood volume monitoring correlate to hemodialysis-associated hypotension?Nephron Clin Pract. 2011;117(3):c179-83
12. Reddan DN, Szczech LA, Hasselblad V, Lowrie EG, Lindsay RM, Himmelfarb J, Toto RD, Stivelman J, Winchester JF, Zillman LA, Califf RM, Owen WF Jr. Intradialytic blood volume monitoring in ambulatory hemodialysis patients: a randomized trial. J Am Soc Nephrol. 2005 Jul;16(7):2162-9

13. Antlanger M, Josten P, Kammer M, Exner I, Lorenz-Turnheim K, Eigner M, Paul G, Klauser-Braun R, Sunder-Plassmann G, Säemann MD, Hecking M. Blood volume-monitored regulation of ultrafiltration to decrease the dry weight in fluid-overloaded hemodialysis patients: a randomized controlled trial. BMC Nephrol. 2017 Jul 17;18(1):238. doi: 10.1186/s12882-017-0639-x.PMID: 28716046

14. Brummelhuis WJ, van Schelven LJ, Boer WH. Continuous, online measurement of the absolute plasma refill rate during hemodialysis using feedback regulated ultrafiltration: preliminary results. ASAIO J. 2008 Jan-Feb;54(1):95-9.

15. Tangvoraphonkchai K, Riddell A, Davenport A. Platelet activation and clotting cascade activation by dialyzers designed for high volume online haemodiafiltration. Hemodial Int. 2018;22(2):192-200

16. Tangvoraphonkchai K, Davenport A. Pre-dialysis and post-dialysis hydration status and N-terminal pro-brain natriuretic peptide and survival in haemodialysis patients. Int J Artif Organs. 2016; 19;39 (6):282-7

17. Booth J, Pinney J, Davenport A. Changes in red blood cell size and red cell fragmentation during hemodialysis. Int J Artif Organs. 2010;33(12):900-5

18. Booth J, Pinney J, Davenport A. N-terminal proBNP--marker of cardiac dysfunction, fluid overload, or malnutrition in hemodialysis patients? Clin J Am Soc Nephrol. 2010;5(6):1036-40

19. Davenport A. Using dialysis machine technology to reduce intradialytic hypotension. Hemodial Int. 2011;15 Suppl 1:S37-42

20. Mambelli E, Mancini E, Santoro A. A continuous and non-invasive arterial pressure monitoring system in dialysis patients. Nephron Clin Pract. 2007;107(4):c170-6

21. Cordtz J, Ladefoged SD. Pulse contour-derived cardiac output in hemodialysis patients. Hemodial Int. 2010;14(1):78-83

22. Keane DF, Baxter P, Lindley E, Rhodes L, Pavitt S. Time to Reconsider the Role of Relative Blood Volume Monitoring for Fluid Management in Hemodialysis. ASAIO J. 2018 Nov/Dec;64(6):812-818. doi: 10.1097/MAT.0000000000000795

23. El-Kateb S, Davenport A. Changes in hydration following haemodialysis estimated with bioimpedance spectroscopy. Nephrology (Carlton). 2016 ;21(5):410-5

24. Nongnuch A, Campbell N, Stern E, El-Kateb S, Fuentes L, Davenport A. Increased postdialysis systolic blood pressure is associated with extracellular overhydration in hemodialysis outpatients. Kidney Int. 2015;87(2):452-7

Figure 1.
(a) A frame showing the external auditory meatus captured by the digital otoscope (all green colour pixel values within the square are averaged to provide one reading for each frame)
(b) Detrended green colour pixel values over 900 seconds, showing the arterial pulsation

(c) Power spectrum of the green colour pixel values; the spectral peak located at 1.055 Hz (heart rate frequency) has a pulse wave amplitude of 0.2898.

Figure 2. Successful detection of arterial pulse wave comparing recordings from the external auditory meatus and finger-tip, and from the sub-group of patients with systolic blood pressure < 100 mmHg. *** p<0.001

Figure 3. Change in weight loss with the dialysis session and change in green light absorption in external auditory meatus

Figure 4. Haemodialysis may lead to a reduction in systemic blood pressure and tissue perfusion. This can be detected by monitoring the amplitude of the arterial pulse wave and change in green light absorption in the external auditory meatus

Table 1. Percentage change from pre-dialysis value. Systolic blood pressure (SBP), diastolic pressure (DBP), pulse pressure (PP) mmHg, external auditory meatus maximum pulse wave amplitude (amplitude) analogue digital units (ADU)., red light pixel absorption (red), green light pixel absorption (green) ADU.
mean ± standard deviation, median (interquartile range). * p <0.05, ** p <0.01, *** p<0.001 vs pre dialysis

variable	start	30	60	90	120	end
SBP	100	97±14	96±14	95±15	95±14	103±17
DBP	100	102±14	102±16	101±14	100±16	98±19
PP	100	94(80-110)	92(80-110)	93(78-113)	91(78-107)	100(87-112)
Amplitude	100	64 (35-117)	50(26-146)*	57(21-133)***	50(26-145)**	75(32-157)
Red	100	100(98-101)	100(98-102)	100(98-102)	100(98-100)	100(98-102)
Green	100	101(99-103)	100(98-102)	100(97-102)	97(97-100)	101(98-102)