33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Alteration of Autonomic Blood Pressure Control during Hemodialysis in Peripheral Vascular Disease Patients

Jasmine Ion Titapiccolo, *Member*, *IEEE*, Sergio Cerutti, *Fellow, IEEE,* Francesco Garzotto, Dinna Cruz, Ulrich Moissl, Ciro Tetta, Maria G. Signorini, Claudio Ronco, Manuela Ferrario, *Member*, *IEEE*

***Abstract*— Blood pressure (BP) response to volume depletion induced by hemodialysis (HD) treatment may be important to understand the pathophysiology of the increased mortality in HD patients with vascular calcification. In the present study a comparison between end stage renal disease (ESRD) patients affected by peripheral vascular disease (PVD) and ESRD patients without PVD was performed. Continuous blood pressure was recorded at the beginning and at the end of HD. BP and heart rate variability (HRV) were analyzed to quantify the autonomic nervous system regulation of heart beat and peripheral resistance. PVD patients showed an increase of pulse pressure (PP) during HD, an altered autonomic peripheral control, a lower sympathetic activity, with respect to ESRD patients without PVD.**

I. Introduction

The blood pressure response to the physiological stress and volume change induced by hemodialysis (HD) treatment may be important to understand the pathophysiology of the increased mortality in HD patients with vascular calcification.

Recent results have demonstrated an association between the decrease of pulse pressure (PP) induced by HD treatment and improved outcomes [1]. The authors have hypothesized a relationship between the ability to decrease PP after an HD treatment to a better overall blood pressure control and lower risk for subsequent cardiovascular outcomes.

The main objective of this work is to assess and study the cardiovascular control in end stage renal disease (ESRD) patients during HD in order to verify the hypothesis of an association between the peripheral vascular disease (PVD) and an altered autonomic control system on peripheral resistance, and to verify an association between an increase of PP *during HD* and this pathology.

The autonomic nervous system (ANS) regulation of heart beat and afterload, i.e. peripheral resistance, was assessed through continuous recordings of arterial blood pressure (ABP) and heart rate (HR). In general, the oscillations of diastolic pressure (DBP) are considered related to the variations in the afterload, pulse pressure oscillations to the variations in stroke volume, the oscillations of systolic blood pressure (SBP) and heart rate to the activity of cardiac baroreflex [2]. Conventional analyses like spectral decomposition were performed. The meaning of the frequency bands of the heart variability (HRV) signal is the following: the low frequency (LF) is associated with ANS sympathetic activity, the high frequency (HF) band indicates the parasympathetic activity. In BP time series analysis, the very low frequency (VLF) is instead related to local control [3][4], e.g. nitric oxide vasodilatatory activity and myogenic regulation, LF to sympathetic activity, whereas HF is mainly associated with the mechanical coupling with respiratory activity.

This work was supported in part by the Fresenius Medical Care Deutschland GmbH.

J. Ion Titapiccolo, M. Ferrario, M. G. Signorini and S. Cerutti are with Politecnico di Milano, Department of Bioengineering, P.zza Leonardo da Vinci 32, 20133 Milano, Italy (e-mail: jasmine.ion@mail.polimi.it, manuela.ferrario@biomed.polimi.it, mariagabriella.signorini@polimi.it; sergio.cerutti@polimi.it).

U. Moissl and C. Tetta are with Fresenius Medical Care Deutschland GmbH, R&D, Daimlerstrasse 15, 61352 Bad Homburg Germany.

F. Garzotto, D. Cruz and C. Ronco are with Dep. Nephrology Dialysis & Transplantation, San Bortolo Hospital, Viale Rodolfi 37, 36100 Vicenza, Italy.

II. Materials and Methods

A. Study design and procedures

This study was an observational, controlled, clinical study. The study was approved by the Institutional Review Board of San Bortolo Hospital and written informed consent was obtained from each subject before enrolment into the study.

Neither dialysis prescription nor medications were changed in the course of the study.

Continuous blood pressure measurement was recorded by the Finometer device (Finapres Medical Systems, The Nederlands). BP was continuously recorded for at least 10 minutes in the first half an hour of HD ($HD_{beginning}$) and 10 minutes in the last half an hour of HD (HD_{end}), always before the reinfusion of the priming volume.

Before each HD treatment, fluid overload (FO) was assessed with a whole body bioimpedance spectroscopy device (BCM, Fresenius Medical Care, Germany). FO is the amount of fluid excess. The BCM monitor uses an extremely wide range of measurement frequencies (5 to 1000 kHz). High-frequency current passes through the total body water (TBW), low-frequency current cannot penetrate cell membranes and thus flows exclusively through the extracellular water (ECW). Physiological ECW can be determined for a given weight and body composition. Fluid overload (FO), expressed in liters, can be calculated from the difference between the physiological ECW expected and the ECW value measured by bioimpedence spectroscopy device [5].

B. Patients population

80 patients were recruited from the dialysis unit of San Bortolo Hospital, Vicenza. Inclusion criteria were age above 18 years old and maintenance hemodialysis vintage of at least 6 months. Exclusion criteria were a dialysis frequency other than three times per week and hospitalization or antibiotic treatments in the preceding 8 weeks.

The patients were divided in two groups according to the incidence/absence of peripheral vascular disease (PVD): Group 1 (G1) is formed by patients affected by PVD, whereas Group 2 (G2) by patients without PVD.

C. Blood pressure analysis

Five minutes of qualified signals for each phase has been extracted. The adopted criteria were: i) absence of marked drifts and ii) limited number of ectopic beats (less than 5%). Beat-by-beat series of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Pressure (PP), were extracted from the continuous ABP signals. The Heart Period (HP), the equivalent of RR interval, was assessed as the interval between the DBP onset time. For each series the mean values were assessed.

The sub-sequences were corrected by means of an adaptive filtering procedure to remove artifacts or ventricular premature complexes [6]. After filtering, the series were re-sampled at 2 Hz [7].

Autoregressive (AR) spectral analysis was performed and power in the 1) very low frequency (VLF, $0.003<f\leq0.04$Hz), 2) low frequency (LF, $0.04,<f\leq0.15$Hz), 3) high frequency (HF, $0.15<f\leq0.4$Hz) bands was computed, as well as 4) total power, 5) LF/HF ratio , 6) LF+HF power, 7) LF% and 8) HF% as suggested in [7].

For each time and frequency domain parameter, the differences between the values obtained at the end of the treatment and the values obtained at the beginning were also assessed. The variation in each parameter is meant to represent the response to HD treatment.

D. Statistical analysis

For each parameter and for each phase, a t-test was performed between the two groups. Paired t-test was performed to identify significant variations between the end and the beginning of the treatment within groups (Δ values). A t-test was also performed between the Δ values of each index between the two groups. Fisher's Exact Test was used for categorical data. A P-value < 0.05 (2-tailed) was considered statistically significant. The normal distribution of data was previously evaluated by boxplot graphs.

III. Results

15 chronic hemodialysis (HD) patients provided reliable BP measurements and concluded the BP protocol. Table 1 reports the demographic data of the included subjects. Patients in G1 resulted older.

TABLE I
PATIENTS DATA AND HD TREATMENT INFORMATION

	G1 (PVD)	G2 (no PVD)	P-value
n	7	8	
Sex (M/F)	6/1	5/3	n.s.
Age [years]	70±9	48±15.1	<0.01
HD Vintage [years]	7.9±10.3	4.7±4.5	n.s.
Diabetes (Y/N)	2/5	1/7	n.s.
Left Ventricular Hypertrophy (Y/N)	4/3	5/3	n.s.
Average UFR [l/h]	0.64±0.24	0.71±0.25	n.s.
Treatment Duration [min]	241±9	235±12	n.s.
Fluid Overload [l]	2.83±1.64	2.41±1.63	n.s.

The values of SBP and DBP are routinely measured *before* and *after the HD treatment* at each session.

The SBP and PP variations as difference of post HD and pre HD values, do not differ significantly between the 15 patients who provided reliable continuous BP measurements and the remaining 64 patients. Data of one patient were lost. Figure 1 reports a picture of the population enrolled for this study in terms of pre and post HD treatment systolic and pulse pressure values.

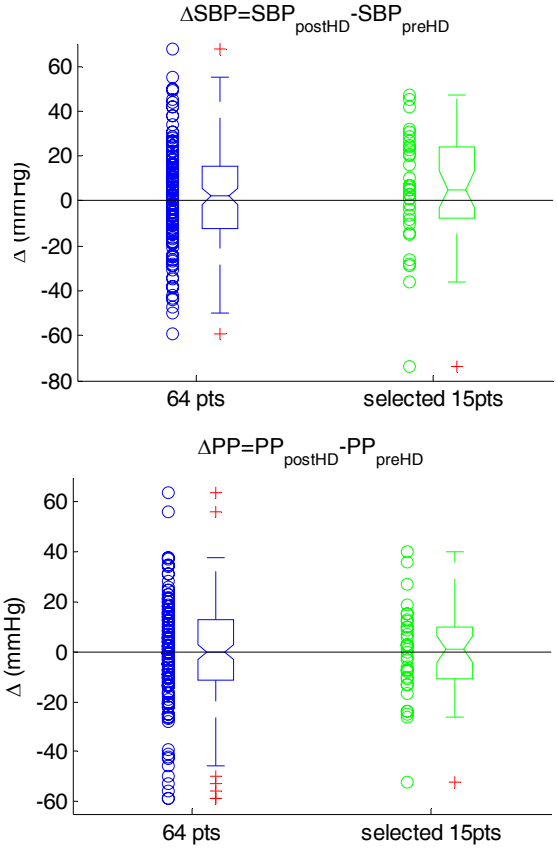

Fig. 1. Upper panel illustrates ΔSBP values and lower panel ΔPP values. The data refers to the values routinely measured before and after HD. For each patient three values of consecutive HD treatment are considered.

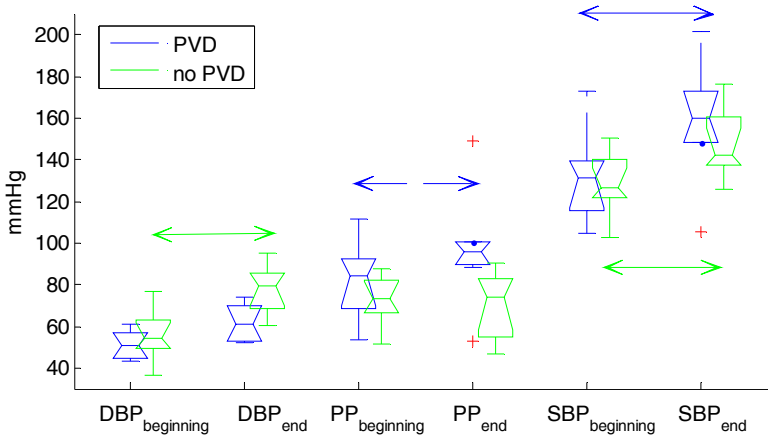

Fig. 2. Boxplot of DBP, SBP and PP values for G1 and G2. The arrows mark the significant comparisons between the values measured at HD beginning and at HD end (paired t-test P-values<0.01 for the solid arrows and P-values<0.05 for the dashed arrow).

As outlined in detail below, G1 and G2 reported a different response to HD treatment.

A. *Time domain parameters*

The HD treatment induced significant variations in BP mean values in both groups. In particular, a significant increase of PP and SBP mean values have been obtained in G1 (PVD), whereas a significant increase of DBP and SBP mean values in G2 (no PVD) (see Fig. 2).

The mean values of PP and HR measured at the end of HD resulted significantly higher and lower respectively in G1 with respect to G2 (PP_{end}: G1 97±28 mmHg, G2 70±16 mmHg; HR_{end}: G1 58±11 bpm, G2 73±14 bpm). The HR values measured at the HD beginning were not significantly different ($HR_{beginning}$: G1 58±7bpm, G2 67± 15 bpm).

The variations of DBP and PP were significantly different between the two groups as well (ΔDBP: G1 9.84±11.70 mmHg, G2 21.91±10.73 mmHg; ΔPP: G1 16.16±14.53 mmHg, G2 -2.68±10.32 mmHg). A significant increase of PP was reported in G1 only, whereas PP in G2 resulted stable or decreased.

TABLE II
MEAN VALUES OF FREQUENCY DOMAIN INDICES

	G1		**G2**	
	Beginning	**End**	**Beginning**	**End**
VLF_{DBP} ($mmHg^2$)	**1060±821***	1249±2031	**380±215**	604±571
$LF\%_{DBP}$	***32± 13***^{*,a}	*55±8*	**58± 19**	54± 15
$LF\%_{SBP}$	***22±8***^{*,a}	*47±16*	**44± 22**	47± 16
$LF\%_{RR}$	***19± 12***^{**,a}	*42±18*	**65± 14**	57± 23
$\Delta LF\%_{DBP}$	**22.7±13.1****		**-4.3±16.2**	
$\Delta LF\%_{SBP}$	**24.6±16.3**$^{\#}$		**3.3±24.3**	
$\Delta LF\%_{RR}$	**22.9±11.6****		**-8.0±20.8**	

T-test * P-value<0.05, ** P-value<0.001, # P-values=0.072 (G1 vs G2)
Paired t-test [a] P-value<0.01 (HD end vs HD beginning)
Δ refers to the differences of the HD end - HD beginning values

B. *Frequency domain parameters*

The HD treatment induced significant variations in the spectral components of BP and HR time series. In particular, a significant increase of LF% values in SBP, DBP and RR has been obtained in patients of G1 (Tab. 2). The VLF values of SBP resulted significantly higher in G1 with respect to G2 at the beginning of HD. The LF% values of DBP, SBP and RR measured at the beginning of HD resulted significantly lower in G1. The variation of LF% of DBP, SBP, RR resulted significantly different between the two groups as well.

C. *Correlation Analysis*

A correlation analysis was performed between the values of the sympathetic components of DBP, i.e. the variation of LF power (ΔLF_{DBP}) and of the normalized LF power ($\Delta LF\%_{DBP}$), and the fluid status of each patient before the HD treatment. A slight negative correlation between $\Delta LF\%_{DBP}$ and FO values was obtained in G2 but not in G1 ($\Delta LF\%_{DBP}$: G1 ρ=0.52, P-value = 0.233; G2 ρ= –0.66, P-value = 0.076).

IV. Discussion

The main finding of the present study is that patients who are affected by peripheral vascular disease (G1) showed a different cardiovascular and autonomic control from patients who are not affected by PVD (G2).

A significant increase of PP has been obtained in G1, whereas a significant increase of DBP in G2. This different behavior seems to be correlated to this pathological condition. In particular, the ability to increase DBP (which is supposed to be correlated to the total peripheral resistance TPR [8]) in response to volume depletion, can be associated with a preserved peripheral control system.

The results from spectral analysis seem to support the idea that the patients affected by PVD (G1) have an altered peripheral control system, on the contrary of patients in G2. In fact, at the beginning of HD G1 showed a lower

sympathetic activity (LF%) on RR, SBP, DBP with respect to G2. Moreover the VLF components of DBP resulted higher in G1, which may be a sign of a prevalence of peripheral local control on the autonomic control [2].

The HD treatment induced a general increase of LF% on RR, SBP, DBP in G1, however not accompanied by a significant increase in HR and DBP mean values. These results may be explained by the presence of peripheral vascular disease, which should produce a chronic elevated afterload, and may be associated with a reduced sympathetic activity on the heart, mediated mainly by cardiopulmonary baroreflex [4], above all when a reduced cardiac baroreflex occurs as in ESRD patients.

A slight negative correlation between FO and $\Delta LF\%_{DBP}$ values was obtained in patients of G2. In particular, the patients with a lower FO reported a higher increase of $LF\%_{DBP}$ values, index which can be considered related to the arterial peripheral vasoconstriction. This result is in agreement with the finding that the fluid status influences the vasoconstrictive response. As illustrated in [9], a protocol of lower body negative pressure, (LBNP) for a controlled simulated hypovolemia, performed before and after saline expansion (25 ml/kg) or before and after volume depletion (administration of fluorosemid) showed that levels of plasma renin activity (PRA) diminished and augmented respectively and the authors concluded that the adequacy of vasoconstriction and pulse pressure conservation depend on the pre-existent volume status.

The limitation of this study was that the PVD patients resulted older than the non-PVD patients. This is mainly due to the fact that PVD have a higher incidence in older patients [12]. However, the alteration of local control and endothelial dysfunction is much more related to PVD pathology than old age condition.

V. Conclusion

The analysis of the autonomic control system during HD allowed to characterize the two groups of patients. Patients affected by PVD, showed a reduced autonomic peripheral control, a lower sympathetic activity on BP and HR, with respect to ESRD patients not affected by this pathology.

The effects of increased PP and atherosclerosis may constitute a feedback loop. Arterial stiffening increases PP, and PP elevation induces endothelial dysfunction. Even though there is no consensus about considering PP reduction as a therapeutic target in the treatment of hemodialysis patients, it seems that a reduction of PP can prevent PVD and it is associated with a better prognosis [10] [11].

Further studies are needed to verify the relationship between FO and vasoconstriction. A prospective study can shed light on the risk of the incidence of PVD in patients characterized by an increase of PP in response to HD treatment or with an elevated PP.

References

[1] Inrig J.K., et al., "Decreased pulse pressure during hemodialysis is associated to improved 6-month outcomes", Kidney Int. 2009 November; 76(10): 1098–1107.

[2] Mukkamala R., Kim J.K., Li Y., Sala-Mercado J., Hammond R.L., Scislo T.J., O'Leary D.S., "Estimation of arterial and cardiopulmonary total peripheral resistance baroreflex gain values: validation by chronic arterial baroreceptor denervation." Am J Physiol Heart Circ Physiol. 2006 May; 290(5): H1830-6.

[3] Baselli G., Porta A., Pagani M., "Coupling arterial windkessel with peripheral vasomotion: modeling the effects on low-frequency oscillations." IEEE Trans Biomed Eng. 2006; 53(1): 53-64.

[4] Aletti F., Bassani T., Lucini D., Pagani M., Baselli G., "Multivariate decomposition of arterial blood pressure variability for the assessment of arterial control of circulation." IEEE Trans Biomed Eng. 2009; 56(7): 1781-90.

[5] PW Chamney, et al., "A whole-body model to distinguish excess fluid from the hydration of major body tissues", Am J Clin Nutr., vol. 85(1), pp. 80-9, 2007

[6] Wessel N., Voss A., Malberg H., Ziehmann C., Voss H., Schirdewan A., Meyerfeldt U., Kurths J.: "Nonlinear analysis of complex phenomena in cardiological data." Herzschrittmacher und Elektrophysiologie 2000; 11: 159-173.

[7] "Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and the North American Society of pacing and electrophysiology." Circulation 1996; 93: 1043-1065.

[8] Bourgeois M.J., Gilbert B.K., Donald D.E., Wood E.H., "Characteristics of aortic diastolic pressure decay with application to the continuous monitoring of changes in peripheral vascular resistance." Circ Res. 1974 Jul; 35(1): 56-66.

[9] Ligtenberg G., Blankestijn P.J., Koomans H.A., "Hemodynamic response during lower body negative pressure: role of volume status," J Am Soc Nephrol. 1998, 9(1): 105-13.

[10] Tozawa M., Iseki K., Iseki C., Oshiro S., Yamazato M., Higashiuesato Y., Tomiyama N., Tana T., Ikemiya Y., Takishita S., "Evidence for elevated pulse pressure in patients on chronic hemodialysis: a case-control study." Kidney Int. 2002 Dec; 62(6): 2195-201.

[11] Dart A.M., Kingwell B.A., "Pulse pressure–a review of mechanisms and clinical relevance. J Am Coll Cardiol 2001 37: 975–984.

[12] Seals DR, Jablonski KL, Donato AJ. Clin Sci (Lond). Aging and vascular endothelial function in humans. 2011 May;120(9):357-75