Furosemide Pharmacodynamics and Cardiovascular Effects in Hemodialysis Patients

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Furosemide is a drug that has not only a renal effect, but also a vascular one, resulting in decreased left atrial and ventricularfilling pressure accompanied by an increase in venous compliance, all of this with significant effects on central cardiac hemodynamics.In dialysis patients, it is still unclear the efficiency of furosemide, a diuretic drug that inhibits the Na+, K+, 2CL" cotransporter in the renal tubular system. Also, furosemide need to be used at much higher doses because of its pharmacokinetic changes in the context of impaired renal clearance.The aim of our study was to investigate whether furosemide induces changes in cardiovascular hemodynamics in end-stage renal disease (ESRD) patients, using standard echocardiography and Tissue Doppler Imaging (TDI).We foundcorrelations between furosemide useand improved cardiac parameters, assessed by multiple echocardiographic variables, and we consider that furosemide has complementary effects in dialysis patients with residual diuresis.

Keywords: furosemide, dialysis residualdiuresis, hemodialysis diuretic

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Diuretics are often stopped when patients start dialysis. Some studies have shown that preserved residual renal function in dialysis patients is associated with bettercardiovascular status and although the association between diuretic and preserved residual renal function is still in debating, the clinical and paraclinical benefits offered by furosemide make it valuable in dialysis patients with urine output [1-3].In dialysis patients,even with someresidual diuresis, furosemide has been shown to induce a rapid vascular effect, besides the diuretic effect. Venous dilatation occurs, and therefore a decrease in cardiac preload and filling pressures[1,2,4]. Several parameters, such as left ventricular hypertrophy (LVH) and left ventricular (LV) systolic dysfunction, have been identified as independent outcome predictorsin dialysis patients [5-7]. Diastolic heart failure and increased filling pressures in dialysis patients often exists without the presence of significant systolic heart failure, and that may be assessed by Doppler techniques, especially Tissue Doppler Imaging (TDI), that has also demonstrated its significant prognostic value for all-cause mortality and cardiovascular death [8-10]. Novel Doppler techniques should be able to detect even more subtle changes in cardiac function induced by furosemide [2, 8-11],

E-wave velocity reflects the left atrium(LA)-left ventricle(LV) pressure gradient during early diastole filling and is affected by impaired LV relaxation andleft atrial pressure(LAP)[8,9].A-wave velocity reflects the LA-LV pressure gradient during late diastole, and it depends by LV compliance and LA contractile function.Mitral E-velocity deceleration time(DT) is influenced by LV relaxation, LV diastolic pressures after mitral valve opening, and left ventricular stiffness.Isovolumetric relaxation time(IVRT) is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRTduration shortens and being inversely corelated with LV filling pressures. [8,9] LA volume index(LAVi) reflects the cumulative effects of increased LV filling pressures and increased LAVi is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke.CW Doppler tricuspid regurgitation(CWTR) systolic jet velocity-significant correlation exists between systolic pulmonary artery pressure(SPAP) and noninvasively derived LAP. Increased SPAP suggests elevated LAP,if pulmonary disease is absent [9,10].E/E'velocity has a powerful correlation with pulmonary capillary wedge pressure (PCWP) compared with invasive measurements of LV filling pressure.Mitral E velocity obtained byPW Doppler complemented using E/e' ratio correlates well to the mean pulmonary capillary wedge pressure (PCWP) as obtained by simultaneous catheter measurements [10,12]. E/E' ratio is a marker of left atrial filling pressure. [9,10,12]

Experimental part

Materials and method

We selected for our study, between January 2015 to December 2016, ESRD patients, who were treated with HD three times a week for more than 6 months, in whom there were some residual diuresis (250 to 650 mL urine/ day). We chose the patients in sinus rhythm, without severe valvular heart disease, ischemic heart disease, congestive heart failure (NYHAclasses III and IV), pulmonary disease or significant pericardial disease.Conventional two-dimensional echocardiography and TDI were recorded with a Siemens Acuson P300, immediately before the dialysis session, therefore cardiac hemodynamics not being influenced by volume or speed ultrafiltration. The echo report was recorded at baseline and further after in similar

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VARIABLE	CONTROL GROUP (N=54)	FUROSEMIDE GROUP (N=47)	P
MALE GENDER, N (%)	38(70,37%)	31(65.95%)	NS
AGE, YEARS (MEAN± SD)	57,21±6.92	54,62±8.81	NS
ETIOLOGY OF RENAL FAILURE, N (%)			NS
DIABETES MELLITUS	21(38.88%)	16(34.04%)	NS
ARTERIAL HYPERTENSION/RENOVASCULAR	17(31.48%)	14(29.78%)	NS
GLOMERULONEPHRITIS	12(22.22%)	8(17.02%)	NS
OBSTRUCTIVE/REFLUX	7(12.96%)	5(10.63%)	NS
POLYCYSTIC KIDNEY DISEASE	2(3.70%)	1(2.12%)	NS
OTHER CAUSES	5(9.25%)	3(6.38)	NS
DIALYSIS VINTAGE, YEARS (*MEAN± SD)*	2.6±1.7	2.4±1.4	NS
DAILY DIURESIS, ML (MEAN±SD)	381.35±80.83	561.36±65.12	< .001
FUROSEMIDE DOSE, MG (MEAN±SD)	-	175.3±62.78	-
AV FISTULA, N (%)	42(77.77%)	35(74.46%)	NS
BMI, KG/M^2(MEAN ±SD)	25.4±3.4	25.5±4.9	NS
BODY SURFACE AREA, M^2(MEAN ±SD)	1.85±0.35	1.81±0.31	NS
DISLYPIDEMIA, N (%)	24(44.44%)	20(42.55%)	NS
CIGARETTE SMOKING	9(16.66%)	8(17.02%)	NS

Table 1
POPULATION BASELINE CHARACTERISTICS

conditions.All patientsbenefited from cardioprotective medications which hadshown to reduce mortality[13] in the general population such as angiotensinconverting enzyme inhibitors, beta-adrenergic antagonists (beta-blockers), acetylsalicylicacid,3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) and cytoprotective anti-ischemic agent [14].Dyslipidemia, measured through blood test, (including high levels of cholesterol, triglycerides, LDLc and low levels of HDLc) is part from thefactors involved in increased cardiovascular risk associated with CKD and also with progression of kidney failure [15]. Furthermore,the variety of biomarkers availabled for monitoring and for the prognosis of acute kidney injury(AKI) are limited, andin present numerous trials have proven the importance of microRNAs in this field[16,17].Standard echo measurements, including left ventricular end diastolic and end systolic dimensions (LVEDD and LVESD), end-diastolic and systolic wall thickness of interventricular septum (IVSd and IVSs) and left ventricular posterior wall (PWTD and PWTS) were determined with the M-mode (Mm) technique. Ejection fraction (EF) was determined using M mode and Simpson method and complemented by *eyeballing* .LV mass was calculated by Devereux's formula using the M-mode of the parasternal long axis view, and indexed to body surface area. LV hypertrophy was defined as LVMI >115 g/m² in men and >95 g/m² in women [8,9]. Left atrium dimension(LAd) was measured as anteroposterior diameter in M mode from parasternal long axis view and also as left atrial volume using bidisc method in the apical four and two chamber view.

LV diastolic function parameters were assessed both conventional and through TDI. Using pulse-wave Doppler(PW) at the tip of the mitral leaflets in the 4-chamber view,mitral E-wave velocity, E-wave deceleration time (DT), and late diastolic wave (A) velocity were measured. Mitral inflow E/A ratio and DT are used to identify the filling patterns: normal, impaired relaxation, pseudo-normal, and restrictive filling [8,9].TDI wasperformed in high frame rate (≥100 frames/second) from the apical four chamber view to assess myocardial velocities. Peak annular early diastolic velocity (E') was measured in annular LV segments (septal and lateral). E/E2 ratio was calculated, and significant LV diastolic dysfunction was defined as E/E' ≥ 14, septal E' velocity <7cm/s, lateral E' velocity<10 cm/s,CW TR velocity> 2.8 m/s and LA volume index(LAVi)>34mL/m² [8,9].E/E' ratio < 8 isassociated with normal LV filling pressures (PCWP < 15 mmHg), while a ratio > 15 is associated with increased filling pressures (PCWP > 15mmHg) [10,12,].

Statistical analysis

Statistical analysis was performed usingGraphPad Software, Inc 3.1. To calculate the statistical significance, we performed comparisons between the two groups using the t-Student test and Fisher exact test. For variables with Gaussian distribution, the values are presented as mean ± standard deviation and p was calculated using unpaired t-Student test. Correlation has been evaluated with Pearson test. Comparisons between baseline and next month measurements were performed using ANOVA with the Turkey post hoc test.Statistical significance was considered if $p<0.05$.

Results and discussions

No patient died or suffered from a major cardiovascular event. In table 1 we can see that there were no significant differences between the group characteristics (gender, age, etiology, dialysis period, vascular acces, BMI, BSA and the presence of other risk factors). There was a significantly better urine output in the furosemide group($p<0.0001$), proportionally correlated to a higher dose of furosemide. None of the patients had normal diastolic function and all of them had LVH withnormal EF(>55%).Also, there were no differences between blood pressure values over time in both groups.All patients were examinated imediatly before dialysis, so they were overhydrated, which was demonstrated by high E/E' values, indicating a CPWP >12 mmHg (E/E'>15). E wave, A wave, E/A ratio, DT, LA parameters and SPAP were higher in the control group and it got worse through time reaching statistical significance($p<0.05$) as seen in Table 2. Regarding TDI parameters we observe in Table 3 that E' wave, A' wave, E/E' ratio are direct proportional, with high PCWP and LV filling pressures. Standard echocardiography and a more sensitive method, TDI, showed that furosemide was able to inducechanges in cardiac hemodynamics also correlated with urine output. Most of the echocardiographic parameters were significantly better in dialysis patients receiving furosemide, as evaluated through time. Furosemide can cause a rapid venodilatory response, which starts before an effect on diuresis and can be notedvia echo parameters [2,18]. Previous studies concerning cardiovascular effects of furosemide have shown different results, due to various methods, vascular status and studied

Table 2

CLINICAL AND STANDARD ECHOCARDIOGRAPHY PARAMETERS IN THE STUDIED GROUP PATIENTS

	Parameter	Baseline	3 months	6 months	9 months	12months	18 months	24 months	P
	EF (%)	61.1±11.0	62.8±13.6	61.3±12.5	60.6±14.4	58.9±15.6	56.7±16.4	57.1±18.5	NS
	FS (%)	37.7±11.5	37.1±13.2	35.3±11.4	36.6±12.2	34.3±10.6	33.5±13.1	34.8±11.8	NS
	E(m/s)	0.9±0.3	1.2±0.5	1.1±0.2	0.8±0.4	1.0±0.1	1.1±0.4	1.2±0.5	< .001
	A (m/s)	0.7±0.4	0.9±0.2	0.7±0.5	0.9±0.2	0.8±0.3	0.6±0.5	0.5±0.4	< .0001
	E/A	1.9±0.8	1.8±1.1	2.0±1.5	2.2±1.8	2.1±2.0	1.9±1.4	2.2±1.2	< .0001
Control	DT (ms)	170.2±25.4	174.9±29.6	167.3±31.8	181.4±41.3	189.2±33.4	193±39.2	191.3±49.5	< .0001
group	LAV(ml)	68.1±17.5	62.1±16.0	76.5±26.2	61.7±13.6	88.8±19.4	71.2±16.3	80.3±29.2	< .0001
	LAd (cm)	3.9±2.6	4.2±1.8	4.5±1.8	4.7±2.7	4.6±2.3	4.4±2.5	4.4±1.4	< .0001
	CW TR(m/s)	2.4±0.6	2.3±0.7	2.6±0.5	2.8±0.8	2.9±0.7	3.2±0.4	3.3±0.5	< .0001
	LVm (g)	191.9±39.5	186.5±26.8	193.3±42.4	195.5±47.1	198.1±47.2	198.6±39.8	210.6±43.1	.0993
	SBP (mmHg)	143.8±22.1	150.0±18.2	152.5±16.2	133.5±74.3	150.4±16.3	148.0±14.3	152.0±14.2	NS
	DBP (mmHg)	82.0±11.0	81.0±9.7	89.4±9.3	79.5±9.8	86.5±10.6	87.0±9.6	89.5±12.5	NS
	EF (%)	62.1±11.6	62.2±8.9	64.3±10.7	60.4±8.5	60.1±18.6	59.2±17.7	59.4±12.3	NS
	FS (%)	38.2±11.8	39.4±9.4	38.1±9.7	37.8±8.9	36.2±11.5	35.7±10.1	35.5±5.0	NS
	E(m/s)	0.7±0.3	0.9±0.2	0.8±0.4	1.1±0.2	0.9±0.2	0.9±0.3	1.0±0.1	.0005
	A (m/s)	0.7±0.2	0.8±0.3	0.6±0.2	0.6±0.3	0.8±0.2	0.8±0.4	0.9±0.1	.005
	E/A	1.1±0.3	1.4±0.5	1.3±0.6	1.4±0.7	1.3±0.6	1.0±0.4	1.4±0.7	.0031
Furosemide	DT (ms)	164.2±23.4	184.9±29.6	187.3±31.8	191.4±41.3	169.2±53.4	173±49.2	181.3±49.5	.0318
group	LAV(ml)	58.1±17.5	62.1±16.0	56.5±16.2	61.7±13.6	58.8±19.4	61.2±16.3	60.3±19.2	NS
	LAd (cm)	2.9±1.1	3.3±1.9	3.5±1.6	4.8±2.0	3.7±1.4	3.5±1.6	3.9±1.1	< .001
	CW TR(m/s)	2.0±0.6	2.0±0.7	2.4±0.5	2.7±0.8	2.6±0.7	2.8±0.4	3.0±0.5	< .0001
	LVm (g)	181.9±35.5	176.6±29.6	190.3±43.2	185.5±48.4	199.1±37.2	189±29.8	201±48.6	.0545
	SBP (mmHg)	143.3±20.5	147.5±22.2	143.7±26.9	145.8±24.0	144.2±21.5	143.8±20.1	141.8±22.8	NS
	DBP (mmHg)	76.2±7.5	70.0±11.5	78.7±10.3	73.7±13.8	79.7±14.9	73.7±14.9	77.9± 17.9	NS

Table 3

TDI PARAMETERS OF LV DIASTOLIC FUNCTION AND LV FILLING PRESSURE IN STUDIED GROUPS. PCWP WAS ESTIMATED USING NAGUEH FORMULA (PCWP = 1.24 * (E/E') + 1.9)

	Parameter	Baseline	3 months	6 months	9 months	12months	18 months	24 months	P
	E´(cm/s)	5.8±1.4	6.3±1.6	5.9±1.5	5.9±1.7	7.1±1.8	6.4±1.6	7.2±1.7	< .0001
	A´ (cm/s)	5.0±2.4	4.6±2.3	4.7±1.9	5.1±1.8	5.6±2.0	5.5±2.1	6.5±2.2	< .001
Control	E´/ A´	0.9±0.4	1.7±1.2	1.5±0.8	2.0±0.5	1.4±0.7	1.6±1.0	1.5±0.5	< .0001
group	E/E´	21.1±18.8	28.8±13.3	22.0±14.5	26.1±14.2	36.0±16.8	31.3±8.1	32.9±18.2	< .0001
	IVRT (ms)	108.9±32.5	95.6±24.2	93.5±23.8	104.2±33.3	109.5±19.3	107.1±21.4	111.4±28.8	< .0011
	ePCWP (mmHg)	15.8±2.7	13.9±1.8	16.8±2.6	17.9±2.3	15.4±2.1	14.1±2.9	18.2± 3.4	< .0001
	E´(m/s)	4.8±1.9	4.5±2.3	5.1±2.1	4.9±1.8	4.7±2.3	4.7±1.3	5.7±2.3	< .0001
	A´ (m/s)	6.4±1.2	5.5±1.5	5.8±1.7	5.7±1.5	6.1±1.8	7.1±1.8	6.6±1.8	< .05
Furosemide	E´/ A´	0.8±0.4	0.7±0.3	0.9±0.5	0.9±0.2	1.1±0.3	0.8±0.3	1.2±0.4	NS
group	E/E´	17.5±7.5	22.2±7.6	24.0±12.9	25.4±11.9	26.3±15.6	19.0±4.9	20.1±6.2	< .0001
	IVRT (ms)	122.6±41.2	118.9±32.3	124.3±36.9	115.4±32.2	121.0±44.7	117.0±34.4	119.0±24.0	<0.01
	ePCWP (mmHg)	11.7±1.6	12.9±2.3	10.4±1.6	13.9±2.5	14.0±2.1	13.1±3.2	13.2± 2.6	<.0001

Abbreviations: EF=Ejection traction, FS=Fractional shortening, E=Early distolic flow velocity, A=Late diastolic flow (atrial kick), DT =Mitral E-velocity deceleration time, LAV=left atrial volume, LAd=left atrial antero-posterior diameter, CW TR=continuous wave Doppler tricuspid regurgitation velocity, SBP/DBP= systolic/diastolic blood pressure, E´=Average of the lateral and septal E' values, IVRT=isovolumetric relaxation time, ePCWP=estimated pulmonary capillary wedge pressure.

populations. Some studies have suggested that furosemide also has extra renal effects, some vascular effects that may justify its use also in anuric patients [2,19]. However, studies evaluating the vascular effects of furosemide in ESRD patients have shown conflicting results. Schmieder published a study in wichan iv bolus of furosemide wasgiven to HD patients [20]. The result was a significant decrease in central blood volume that was seen minutes after the bolus, indicating a redistribution of blood from the cardiopulmonary system to the periphery [20]. Other authors demonstrated that after an intravenous dose of furosemide left ventricular fillingpressure decreased. It's important to understand that there is much more to an echo exam than *mere EF* [5]. eGFR value alone-demonstrated that is a better follow-up parameter then EF, as a marker for cardiovascular morbidity and mortality [21].So, in this special population we have to come with something more in orderto add more prognostic value. The novel tissue Doppler and Speckle tracking techniques can guide us to understand and treat the complex patient involved in this pathophysiological relation between kidney and heart [8-12].Also, in most studies, arterial stiffness is assessed by carotid-femural pulse wave velocity (cfPWV), andwould have been a useful markerbecause it is correlated with overall mortality and cardiovascular mortality,even in dialysis patients[22]. Furthermore, we emphasise the need for more large-scale randomized studies in dialysis patients and comprehensive cardiovascular guidelines for their management [2,23].

Conclusions

The aim of this paper was to demonstrate whetherdiureticshould be continued on hemodialysis patients with some residual diuresis, even after they have been on dialysis for a period of time.For the specifichemodialysis population, adose of furosemide, can significantly improve echo parameters, it reduces the weight gainbetween dialysis, may result in better blood pressure values and possible lower the risk of heart failure and improved symptoms. Furthermore, there may be a favorable impact on cardiac hemodynamics, probably both by vascular and renal effects.

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