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Narrative Review

Use, misuse and abuse of diuretics

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ABSTRACT

Resolution of edema requires a correct interpretation of body fluids-related renal function, to excrete the excess volume while restoring systemic hemodynamics and avoiding renal failure. In heart failure, the intensive diuresis should be matched by continuous fluids refeeding from interstitium to plasma, avoiding central volume depletion. The slowly reabsorbed ascites cannot refeed this contracted volume in cirrhosis: the ensuing activation of intrathoracic receptors, attended by increased adrenergic and Renin release, causes more avid sodium retention, producing a positive fluid and Na balance in the face of continuous treatment. High-dose-furosemide creates a defect in tubular Na causing diuresis adequate to excrete the daily water and electrolyte load in Chronic Renal Failure.

Diuretic treatment requires care, caution and bedside "tricks" aimed at minimizing volume contraction by correctly assessing the homeostatic system of body fluids and related renal hemodynamics.

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Table 1
Glossary of acronyms and abbreviations.

ADH = anti-diuretic hormone	HL = Henle's loop
ANP = atrial natriuretic peptide (also called BNP)	ICU = intensive care unit
ARF = acute renal failure	ICV = intra-cellular volume
BB = brush border	K^+ = potassium ion
BW = body weight	LC = liver cirrhosis
CA = carbonic anhydrase	MD = Macula Densa
CD = collecting duct	Na^+ = sodium ion
CHF = congestive heart failure	NS = nephrotic syndrome
Cl^- = chloride ion	PA = arterial pressure
CO = cardiac output	PG = prostaglandins
CRF = chronic renal failure	PT = proximal tubule
CSF = cerebro-spinal fluid	PCr = plasma creatinine concentration
CVP = central venous pressure	PV = total plasma volume
DHCT = dihydrochlorothiazide	q.d. = once daily; b.i.d = twice daily; t.i.d. = 3 times daily; q.i.d. = 4 times daily;
DT = distal tubule	q.o.d. = every other day
ENaC = epithelial Na channel	RAAS = renin-angiotensin-aldosterone system
ECV = extra-cellular volume (also, ECF)	RTA-IV = renal tubular acidosis type four
EDLVV = end-diastolic left ventricular volume	TF = tubular fluid
EffPV = effective plasma volume	TP = total protein concentration
ERSD = end-stage renal disease	UNa = Urinary Na^+ concentration
F = furosemide	UK = Urinary K^+ concentration
FENa = fraction of filtered Na^+ which is being excreted	UH = Urinary H^+ concentration
GFR = glomerular filtration rate	UOsm = urine osmolarity
GTB = glomerulo-tubular balance	$\dot{V}$ = urine flow rate
HCO_3^- = bicarbonate ion	
HF = heart failure	

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1. Pathophysiology of edema formation and action of diuretics

Table 1 illustrates the abbreviations used.

Edema, an excess volume retention causing clinically recognizable interstitial expansion, is treated with diuretics summarized, by selected data [1–15], in Table 2. This paper deals exclusively with treatment of edema, it will not mention mercurial diuretics and aquaretics, nor treatment of other derangements. The normal body fluid homeostasis and its alterations generating edema, as well as the related factors controlling the effectiveness of diuretics, can be understood by examining Fig. 1a. The EffPV is the volume contained inside large intrathoracic vessels: when reduced, the vessel walls trigger sympathetic outflow-RAAS, leading to Na retention and edema formation till the volume lost has been replenished inside thoracic vessels [16]. The opposite occurs when the EffPV is increased. Na retention or rejection will be dictated, independent of total-body-PV [17], only by the EffPV status, which also acts as

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FIGURE 1a - BODY FLUIDS HOMEOSTASIS

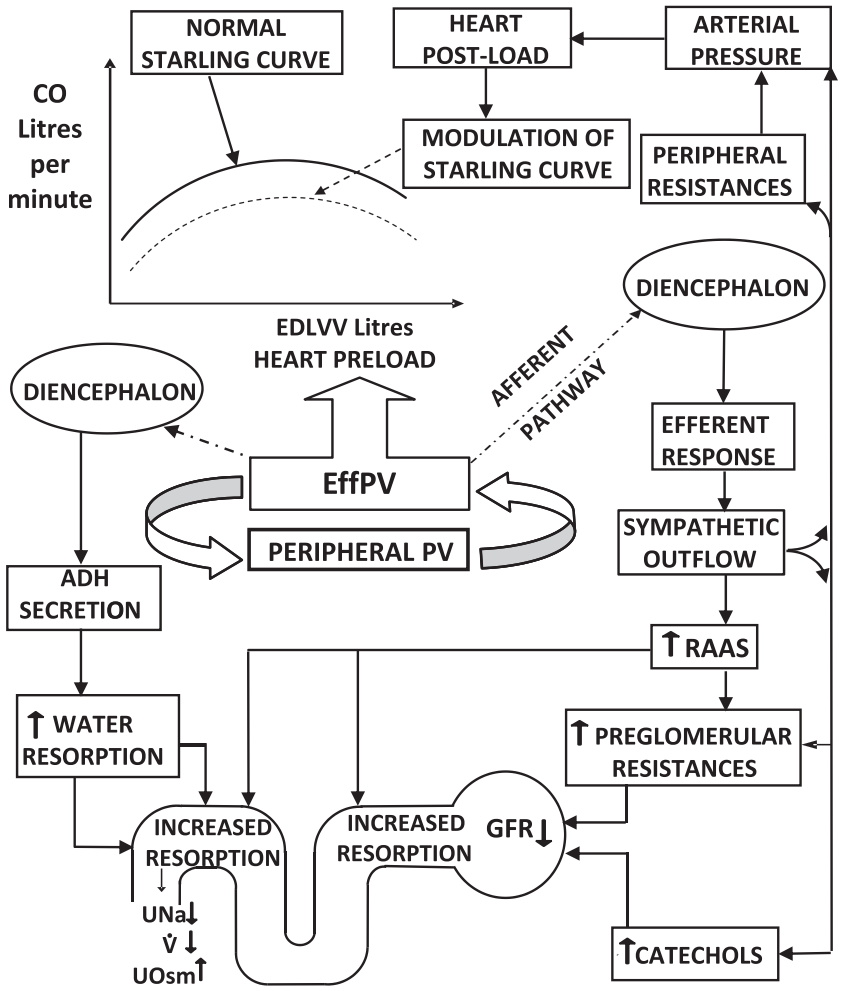

Fig. 1a. - Body Fluids Homeostasis. The Figure illustrates the homeostatic control of Na excretion. The response to volume depletion is portrayed: although not shown, a reverse sequence of events takes place during volume expansion. In the center two rectangles indicate the peripheral plasma volume (PV) interconnected with the effective plasma volume (EffPV), which is contained in the intra-thoracic vessels. The arrow pointing from this to the abscissa of the Starling relationship indicates that the EffPV is a component of cardiac preload. The preload constitutes, as end-diastolic left ventricular volume (EDLVV, in litres), the abscissa of the Starling function, having the cardiac output (CO in Litres/minute) in the vertical axis. The actual line depicting the Starling curve is arbitrary and only qualitatively indicative. The EffPV, through the dashed arrows, fires at diencephalic centers: when it is contracted by dehydration it triggers ADH secretion, that causes water retention, sympathetic outflow and RAAS activation. Catecholamines control blood pressure, and, through it, the cardiac post-load, as well as renal vascular resistances. RAAS controls renal vascular resistances and distal Na reabsorption. Both concur in causing reduced filtration and enhanced Na/water reclamation from the nephron, ending in Na retention and edema formation. Only these two efferent branches of the homeostatic system are portrayed for simplicity. The arrows on the side of UNa (urinary Na concentration), $\dot{V}$ (urine flow rate) and Uosm (urine osmolality) indicate high values when pointing upward, reduced values when pointing downward. Modified from Bartoli E. Medicina Interna: Metodologia, Semeiotica, Fisiopatologia, Clinica, Terapia Medica. R.A.H.P sas, 2010, ISBN 9788890438110, with permission of the Editor.

the heart preload, determining CO according to the Starling relation. This leads to different pictures:

I – Low EffPV-low CO: the preload works on the ascending part of the Starling curve (Fig. 1b-I). The afferent stimuli from intrathoracic vessel walls act synergistically with those generated by low CO to activate the Na-retention pathway. The kidney responds poorly to diuretics by limiting Na supply to the resorption sites where the drugs act. This picture is typical of LC, where a fraction of PV is "trapped" inside the splanchnic district, because of the rise in sinusoidal resistances. This fraction is subtracted to the EffPV, which is therefore correctly sensed as reduced by central receptors, dictating Na-water retention [16–19]. The Na-retaining effect of LC was reproduced by increasing interstitial pressure in an intact liver through a rise in thoracic duct pressure, in the absence of peripheral vasodilation, pointing to EffPV depletion as the cause of Na retention [20]. Vasodilation, when present, acts as an arteriovenous fistula [21]: it unloads the central volume, causing renal vasoconstriction, attended by Na-retention, like that determined by low CO. The volume retained is preferentially dissipated as ascites because of the favorable conditions for filtration into the peritoneal cavity by the increased sinusoidal and peritoneal capillary pressures. As the retained volume does not participate to heart preloading and to intra-thoracic vessel wall receptor stretching, it does not switch off the Na-retaining alteration of the homeostatic system, such that the kidney keeps retaining Na-water.

The diuretic treatment of this edema worsens EffPV contraction, enhancing the sympathetic outflow if the diuresis exceeds the rate of ascites reabsorption. Also, it will reduce heart preload and CO by shifting the abscissa of Starling function to the left, towards lower filling volumes (downward arrow pointing to the left in Fig. 1b-I). The ensuing ARF [19] is caused by a normal functioning kidney that reacts as if the overall-PV had fallen [22], being wrongly informed by stretch receptors. Large volume paracentesis frequently worsens the Na-retaining asset of the nephron because ascites formation

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