Fluid Overload in Peritoneal Dialysis Patients

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Summary: Volume management in peritoneal dialysis patients is of importance, as both volume overload and dehydration are associated with worse outcomes. When assessing volume status, it is important to understand that different techniques measure different fluid compartments (intracellular vs extracellular vs circulating volume) and the impact of cardiac function. Attention to salt restriction and diuretics can help to maintain euvolemia without need for hypertonic bags. Glycaemia should be monitored to avoid thirst. Dwell length should be adapted to transport status: short dwells for fast transporters, long dwells in slow transporters. The role of bio-compatible solutions on volume control remains controversial.

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When discussing fluid status in peritoneal dialysis (PD) patients, it is important to remember that fluid can accumulate in different compartments. It is most important to make a distinction between intracellular and extracellular water, whereby the latter is to be divided in the circulating and interstitial compartments. Intracellular water (ICW) is associated directly and linearly with muscle mass. In adipose tissue, the obligatory associated water is found mainly in the extracellular compartment, which results in an increasing extracellular water to total body water (ECW/TBW) ratio because fat mass goes up in obese people, and this is irrespective of hydration status. Fluid volume in the circulating compartment is most relevant for direct cardiovascular consequences, mainly hypertension and pulmonary congestion. The causes and clinical consequences of fluid accumulation might be different between these different compartments, and the method used to assess the fluid status also will impact which compartment mainly is targeted and thus will influence the final results, explaining in part the poor correlation between the different methods to assess volume status.1 It thus is important to take into account which compartment has been assessed when interpreting results or making clinical decisions based on assessments of volume status.2

Evidence points out that in PD patients, fluid overload is present mostly in the extracellular non-circulating compartment.2

It also is important to use consistent terminology when talking about fluid status of PD patients.3 Fluid balance is the difference between the volume of dialysis fluid drained from and that instilled into the patient. It should not be used to indicate the absolute fluid status/hydration status of the patient. Overhydration, normohydration, and dehydration should be used for qualitative descriptions of fluid status, whereas fluid overload in liters is suitable to quantify the amount of overhydration (positive number) or dehydration (negative number).3 Volume status should be used only to qualitatively describe the fluid present in the circulating (plasma) compartment.

EPIDEMIOLOGY OF FLUID STATUS IN PD

Fluid overload (FO), common in PD patients, is linked directly to increased cardiovascular (CV) morbidity and mortality. Congestive heart failure, which accounts for approximately 5% of all-cause mortality in prevalent dialysis patients, is associated closely with fluid overload, although other major CV events also could be affected by it.4 However, volume control is a modifiable risk factor.5

Adequacy of peritoneal dialysis in Mexico (ADEMEX) showed no survival advantage of an increased dose of small-molecule clearance delivered by PD, but found an association of fluid overload and mortality.6 All these have shifted the focus of dialysis adequacy from small-solute clearance to volume control.7 The International Society of Peritoneal Dialysis (ISPD) guideline recommends regular clinical assessment of hydration status. It also recommends that hypertensive PD patients should have their volume status optimized before starting an antihypertensive treatment.8

Fluid status in PD patients can be assessed in different ways, and the prevalence of fluid overload varies depending on which method was used. The initiative for patient outcomes in dialysis - peritoneal dialysis (IPOD-PD) study of 1,092 patients from 135 centers in 32 countries investigated the baseline hydration status in...
FLUID STATUS IN PD VERSUS HEMODIALYSIS

Peritoneal dialysis provides slow but continuous ultrafiltration. This might be an advantage because it might imply an improved quality of life for patients to be allowed a relatively liberal dietary intake of salt, potassium, phosphate, protein, and fluid. However, in the opinion of most clinicians, fluid overload is thought to be more common in PD than in HD patients. In contrast to this widespread belief, most studies comparing peritoneal versus hemodialysis patients find that fluid overload is similar in both modalities. However, in other studies, fluid overload was more expressed in PD versus HD patients. In one cross-sectional study of 76 prevalent patients (43 HD and 33 PD), the OH/ECW ratio assessed by the bioimpedance spectroscopy device was significantly higher in PD patients compared with post-HD patients. In another cross-sectional study of 104 prevalent patients, FO was even slightly more expressed in PD compared with pre-HD. The relationship between fluid status as estimated by bioimpedance analysis and plasma albumin is different between PD and HD patients. Although worsening of fluid status as determined by BIA was correlated strongly to a reduced plasma albumin level in both dialysis modalities, the association was much stronger in PD patients.

To date, it has not been clarified why maintenance of euvolemia seems to be less easy in peritoneal dialysis as compared with HD. A lower compliance rate with dietary salt and fluid restriction has been suggested, because thirst is more common in PD. Diabetes further aggravates thirst distress in PD patients, explaining the increased rate of FO in diabetic PD patients. Furthermore, although HD patients normally make routine visits of three times a week and have their fluid volume and dry weight controlled, stable PD patients make less than one monthly contact with the health professionals.

The 24-hour sodium removal was higher in CAPD versus automatic PD (APD) patients, and there was a trend toward better hypertension control in the CAPD group. This may result in a difference in volume status. However, no reliable data are available to support the presence of a difference in fluid status between APD and CAPD. In an observational, cross-sectional study of 158 prevalent patients (90 CAPD, 68 APD), there was no difference in the extracellular fluid volume (ECF)/TBW ratio between CAPD (51.8%) and APD (51.9%) patients (P = .929). In another cross-sectional study of 200 prevalent patients assessed by bioimpedance spectroscopy, there was no difference between CAPD and APD in ECF volume, height-adjusted ECF volume, or the ECFV/TBW ratio. CAPD was shown to be superior to APD in evaluation of left ventricular mass index and ultrafiltration.

CLINICAL CONSEQUENCES OF FLUID STATUS IN PD

Fluid overload in peritoneal dialysis patients is associated with mortality, particularly CV mortality. The overhydration index as measured by bioimpedance spectroscopy was an independent predictor of mortality when body mass index and lean tissue index were included in a multivariate model. In a cross-sectional study, fluid overload as assessed by bioimpedance was an independent predictor of all-cause mortality and technique failure in CAPD patients. In a retrospective study of 227 incident PD patients, ECF/intracellular fluid (ICF) was a strong predictor of survival, with a relative risk of death of 1.4 for every increment of 0.1 in the ECF/ICF value (Fig. 1).

Hypervolemia, identified by the inferior vena cava index, decrease of inferior vena cava diameter on deep inspiration (collapsibility index), and anemia contributed independently to left ventricular geometry in CAPD patients. PD patients with fluid overload tend to have increased left ventricular mass index, left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and decreased left ventricular ejection fraction and fractional shortening. Sustained...
normovolemia by salt restriction and ultrafiltration was associated with a reduced incidence and regression of left ventricular hypertrophy. In randomized open-label studies, a reduction of fluid overload resulted in a significant reduction in left ventricular mass, suggesting that left ventricular hypertrophy is modifiable by improving volume control in peritoneal dialysis patients.32,33 Fluid overload was related to diastolic dysfunction, a sensitive and independent indicator of future major adverse cardiovascular event (MACE) in PD patients.34

High N-terminal pro-brain natriuretic peptide (NT pro BNP) and cardiac troponin (cTNT) levels, reflecting left ventricular dysfunction and fluid overload, were associated with sudden cardiac death.35 Additional fluid removal and strict volume control improved the BNP level in incident hypertensive dialysis patients.36 Fluid overload also is related closely to significant comorbidity and quality of life in PD patients. Uncontrolled hypertension and increased inflammatory markers are more common in PD patients with fluid overload than in those without. Fluid overload also has been associated with sleep apnea and nutritional status, with a lower nutritional index and more frequent malnutrition in those with FO.

Although the ECW content in hypertensive dialysis patients is significantly higher in general than in normotensive dialysis patients, a wide variability in blood pressure regardless of the degree of hydration status has been observed in PD patients.38 In an observational prospective cohort study, a significant increase in fluid volume was not linked to a significant increase in blood pressure. Rather, the change in the total peripheral resistance was found to be the most important determinant of the extent to which increased fluid volume affected blood pressure.39 In the Brazilian PD (BrazPD) cohort, edema control improved hypertension.40 Strict volume control by dietary salt restriction and ultrafiltration decreased mean blood pressure from 138.4 ± 29.9 and 86.3 ± 16.8 to 114.9 ± 32.3 and 74.7 ± 18.3 mm Hg, respectively, in a 10-year follow-up study.41 In addition, fluid overload disrupts circadian variation of blood pressure, a common finding in PD patients. Reduced blood pressure variation was associated with left ventricular mass index in PD patients. Patients with chronic fluid overload tend to have increased mean carotid artery intima-media thickness.42

Bioimpedance spectroscopy–based fluid overload was an independent predictor for technique failure and peritonitis in CAPD patients.43 In a randomized controlled trial of 41 patients with diabetic nephropathy with end-stage renal disease, icodextrin increased technique survival by improving body fluid management over a 2-year follow-up period.44 Strict volume control by dietary salt restriction and ultrafiltration led to a better technique survival during the first 3 years, but not after 5 years in a 10-year follow-up study.41

Fluid overload has been associated with an increased duration of hospitalizations.45 Longitudinal changes in the cardiothoracic ratio for 12 months on routine chest radiographs were an independent predictor of hospitalization-free survival.46

Because volume depletion has been linked to acute kidney injury and a rapid decrease of residual renal function (RRF), some have advocated mild fluid overload for preservation of residual renal function. According to the reported data, however, both overhydration and dehydration were associated with residual renal function decrease, whereas maintaining adequate volume status was shown to aid with RRF preservation.32,35 Changes in residual renal function and ECW/TBW as measured by bioimpedance spectroscopy in 237 adult patients who had paired baseline and serial 12 monthly measurements showed that increased ECW/TBW in PD patients was not associated with preservation of RRF, whereas increments or decrements in ECW/TBW were not associated with preservation or reduction in RRF.47,48 A threshold value of optimal hydration to preserve residual renal function needs to be elucidated.

**DRIVING FACTORS OF FLUID STATUS IN PD PATIENTS**

The fluid status of PD patients can be influenced by patient-related and by PD-related factors (Fig. 2).

**Residual Renal Function**

Residual renal diuresis was not related to fluid status as assessed by bioimpedance measurement in a large observational cohort of prevalent European PD patients.10 Renal clearance but not urinary volume determined fluid status in a US-based cohort,24 whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.11 In incident PD patients, urinary output was associated with fluid status in the univariate, but not in the multivariate, analysis, whereas in a Chinese prevalent cohort, less urinary output was associated with overhydration.
water intake. Such liberal fluid intake might become problematic when residual diuresis eventually starts to decrease. Second, it has been argued that patients should be kept slightly overhydrated to preserve residual renal function because this has been associated with improved outcomes. However, retrospective observational data with their inherent methodologic limitations seem to indicate that an increased ECW/TBW ratio was not associated with preservation of residual renal function. Even anuric patients can

Figure 2. Modifiable and nonmodifiable factors influencing fluid status. BMI, body mass index.
maintain normohydration. There is discussion on the role of blockers of the renin-angiotensin-aldosterone system axis. A recent Cochrane analysis identified 6 open-label studies on this topic. Long-term (>12 mo) use of renin-angiotensin-aldosterone system blocking agents was associated with better preservation of residual renal function in patients on peritoneal dialysis as compared with other antihypertensive drugs. There was insufficient evidence to form a preference between angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors.

Salt and Fluid Intake

Hyperosmolarity is a main driver of thirst and thus of water intake. Hyperosmolarity in PD patients can be caused by, among other factors, salt intake or poor glycemic control. Based on physiology studies, increasing sodium intake will result in a (temporary) increase in total body water, especially in the extracellular compartment. Recently, nonsomotic storage of salt in the skin has been unraveled as a mechanism used by the body to avoid fluid overload by salt intake. However, this mechanism also explains the well-established long lag time between the start of a sodium-decreasing strategy and the clinical consequences such as decreased blood pressure because the stored salt gradually is released again in the circulation. As long as residual urinary output is maintained, either spontaneously or by using diuretics, the kidney will compensate the salt and fluid overload by inducing pressure diuresis. As residual renal function decreases, total salt removal also will decrease, and might result in fluid overload. A high salt intake also will induce changes in the peritoneal membrane that might jeopardize proper ultrafiltration. Restriction in salt intake results in better volume and blood pressure control in PD patients. In a Cochrane review, salt restriction in patients with advanced chronic kidney disease was associated with improved blood pressure control.

Poor glycemic control also will result in hyperosmolarity. Diabetes therefore has been associated with increased odds of overhydration both in prevalent as well as in incident patient cohorts. Because hypertonic exchanges induce hyperglycemia, this might explain why patients using hypertonic exchanges remain overhydrated in observational studies. In addition, use of hypertonic bags amplifies sodium sieving, resulting in more removal of free water but not of sodium, thus contributing to the hyperosmolarity and fluid overload. Of note, hyperglycemia might induce hyperinsulinism, which in turn will enhance tubular sodium reabsorption. Although use of hypertonic exchanges has been associated with fluid overload in prevalent patients, a randomized trial to assess the use of glucose-sparing regimens concluded that patients on the glucose-sparing regimen had an increased risk for extracellular volume expansion despite an overall improvement of glycemic control.

Besides the direct effects through hypertonicity, chronic hyperglycemia also leads to changes in the peritoneal membrane such as neo-angiogenesis, leading to ultrafiltration failure. At least in animal models, correcting hyperglycemia results in avoidance of these diabetiform alterations of the peritoneal membrane.

Inflammation and Nutritional Status

In general, PD patients tend to have a lower lean tissue mass and a higher fat tissue mass than the healthy reference population. Because water associated with fat tissue is nearly exclusively extracellular, and because lean tissue mass is associated with intracellular water, the increased ECW/TBW ratio in dialysis patients thus partly could be artificial and unrelated to true fluid overload. In the BRAZPD cohort, an increase of body mass index over time was associated with fluid overload, but also signs of wasting.

There is an association between overhydration on the one hand and hypoalbuminemia and inflammation on the other hand. Fluid overload has been associated with both hypoalbuminemia and low hemoglobin level. Although it is tempting to speculate that these observations are caused by dilution, there was also an association with C-reactive protein levels and protein energy wasting, pointing out that inflammation also could be the common denominator. Demirci et al showed an association between height-adjusted ECW and serum C-reactive protein levels. Interestingly, endotoxemia and peritoneal protein clearance also have been associated with signs of fluid overload, inflammation being the most likely common underlying factor.

Although hypoalbuminemia is a hallmark of fluid overload in PD patients, this overhydration is not associated with increased plasma volume, and accordingly cannot be attributed merely to dilution. Also of interest in kwashiorkor, there is a missing link between overhydration and hypoalbuminemia. For several reasons, it is plausible that disturbance of the glycocalix function, whether or not by inflammation, might cause the capillaries to become more leaky, leading to hypoalbuminemia and interstitial edema.

In addition, endothelial dysfunction as assessed by flow-mediated dilatation has been linked to fluid overload in CAPD patients. Flow-mediated dilatation-assessed endothelial dysfunction, sex, serum albumin, and FO were independent determinants of edema status in PD patients.

Small-Solute Transport

The concept that fast transport status is linked to overhydration is well established in the minds of many
in the field of PD. The explanation seems obvious because fast transporters have a rapid dissipation of their glucose gradient, and thus negative ultrafiltration during longer dwells. Therefore, for fast transporters short dwells are recommended, and APD, with its short dwells, might lead to better outcomes for this patient group. In observational trials, fluid overload is slightly higher in fast transporters compared with other transport categories, but with a wide range, pointing out that other factors, such as adapted prescription regimen and dietary intake, are at least as important. To underline the impact of prescription, fluid overload was highest in patients in whom the transport status was unknown, and in whom, by consequence, the prescription could not be adapted to transport status. It often is neglected that an inapt prescription also can cause overhydration in slow transporters. Too short dwells can induce sodium sieving in slow transporters, and thus lead to removal of free water but not of sodium, resulting in fluid retention. Adaptation of the dwell length to the transport status of the patient is thus a necessity to maintain normohydration.

Fast transport status can be caused by inflammation, which in itself is linked to overhydration. In incident patients, even before the start of PD, fast transporters tended to be more fluid overloaded than other transport categories. This underscores that there are non–PD-related common aspects to overhydration and fast transport status, most likely inflammation.

Impact of Dialysis Solutions

Since the first introduction of biocompatible solutions there has been a signal that they resulted in lower ultrafiltration as compared with nonbiocompatible ones. This observation was against expectations because the lower glucose degradation product (GDP)-containing solutions, and especially the bicarbonate-based ones, have been associated with lower vascular recruitment in rat models. A recent Cochrane review identified 36 eligible studies on this topic, including a total of 2,719 patients. Overall, the study quality was rather low because allocation methods and concealment generally were incompletely reported. The use of neutral pH–low GDP PD solutions resulted in greater urine output and higher residual renal function when used for longer than 12 months. There was a trend for decreased ultrafiltration after a 4-hour dwell when using low-GDP versus conventional solutions. This decreased ultrafiltration also was present when evaluated over a 3-month period, but was no longer present when analyzed over 12- and 24-month periods of evaluation. More recently, Szeto et al showed in a randomized study that low-GDP solutions induced less ultrafiltration and more fluid accumulation in the initial stage, but not in the longer term, whereas Lichodziejewska-Niemierko et al found overhydration and lower ultrafiltration with low-GDP solutions even after 24 months.

In the Cochrane review by Cho et al, prescription of icodextrin was associated with improved peritoneal ultrafiltration and mitigated uncontrolled fluid overload. Although the use of icodextrin for the long dwell increases ultrafiltration, especially in fast transporters, the effects on the residual renal function can be variable, depending on the underlying fluid status of the patient. The impact on fluid status also can be variable, depending on adherence to dietary restrictions.

CAPD Versus APD

Observational studies have shown that there is no difference in sodium removal or volume control in patients on APD versus CAPD. However, in both of these cohorts, APD was performed with a low number of cycles, avoiding too short dwell times and sodium sieving. Indeed, other studies clearly have shown that too short dwells (and too high a number of cycles) are associated with decreased sodium removal. This is especially so in patients with membranes with slower transport characteristics.

ASSESSMENT OF FLUID STATUS

Different methods can be used to assess the fluid status of the patient. As described in the introduction, it is important to realize that each method targets determination of fluid in (a) specific compartment(s). There is a need for formal assessment of fluid status because clinical observation alone is insufficient to correctly identify minor deviations from normohydration. Clinical observation has a high specificity but a low sensitivity for overhydration, and up to 30% of patients who are labeled as normohydrated appear to be overhydrated when a formal assessment is performed.

Serum Biomarkers

BNP is used as a prognostic indicator for mortality, but also has been put forward as a marker of fluid status. It is important to realize that BNP mainly reflects filling pressure of the left atrium, and thus cardiac congestion. As such, BNP reflects a mix of cardiac dysfunction and circulating volume overload. BNP also partly is cleared by dialysis and to a small extent by the kidneys, and this might bias the interpretation of values over time and cause an absence of a clearly defined reference range. As a consequence, in hemodialysis, the performance of BNP as a marker of fluid status has been found to be poor. In PD patients, it has been found to be a good reflection of
right ventricular end-diastolic pressure, but proof of its clinical usefulness is limited.

**Lung Ultrasound**

Lung ultrasound can be used to assess the extravascular water content of the lungs. It is based on a semiquantitative appreciation of the presence of reflections (called comets) observed during an ultrasound examination of the lungs. Accordingly, the technique merely reflects pulmonary wedge pressure, and thus left ventricular preload and circulating volume in relation to cardiac function rather than fluid status per se. The technique has been used in hemodialysis and peritoneal dialysis patients. In the latter study, lung congestion as assessed by lung ultrasound correlated strongly with left ventricular ejection fraction, but not with the presence of peripheral edema, indicating that indeed mainly circulating volume and cardiac function are targeted by the technique. Paudel et al showed that bioimpedance, BNP, and lung ultrasound provided different information, whereby BNP and lung ultrasound mainly indicated left ventricular failure. Siriope et al associated lung ultrasound with mortality in hemodialysis patients, but this was a cross-sectional non-interventional trial, and thus it is very likely that pulmonary congestion is just a consequence of underlying heart failure, being the true driving cause of worse outcome.

**Bioimpedance Measurement**

Bioimpedance analysis (BIA) uses a flow of electrical current through the body tissues to assess body composition (Fig. 3) based on measured impedance, in itself a compound of resistance and reactance. Single-frequency BIA uses only one frequency of current, whereas bioimpedance spectroscopy uses multiple measurements at multiple frequencies. This allows extrapolation (the theoretical) of impedance at zero frequency (corresponding to extracellular water) and at infinite frequency (corresponding to total body water). Resistance is related to water content, whereas reactance is related to integrity of the cell membrane. As such, bioimpedance allows not only assessment of water content of the body, but also cell mass (intracellular water). Different mathematical models can be used to convert the measured impedance to values of body composition. Two-compartmental models are sufficient for estimating fat mass, but three-compartmental models perform better for estimation of fluid status. Each of these models has to be calibrated and validated in a specific population with a specific relation between parameters of body composition as measured with a golden reference standard and bioimpedance. The more characteristics the patient has that deviate substantially from that of the reference population, the greater the chance that the bioimpedance measurement results will be less reliable. As such, results always have to be interpreted by also taking clinical circumstances into account.

All models, however, presume that the body is composed of 3 linked cylinders: the arm, the leg, and the trunk. Because resistance is related inversely to the diameter of the cylinder, the arm and the leg will contribute the most (>90%) to the measured impedance, whereas the trunk will have only a minor

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**Figure 3.** Principles of bioimpedance and bioimpedance spectroscopy.
Diuretics can be used to increase urinary output of water and salt. However, it should be realized that the enhanced excretion of salt with diuretics is only short-lived and that after a couple of days, a new equilibrium will be reached. The use of diuretics also might have a negative impact on residual renal function.

Use of hypertonic exchanges can increase the ultrafiltration volume. The impact on residual renal function and volume balance, however, can be variable, depending on the underlying fluid status and cardiac function of the patient. There is also the risk of enhanced fluid intake because both hyperglycemia associated with poor glycemic control with hypertonic bags, similar to hypernatremia associated with sodium sieving, can increase thirst. It also should not be neglected that use of hypertonic exchanges will lead to more rapid deterioration of peritoneal membrane function, and potentially also of residual renal function.

Icodextrin can be used to increase ultrafiltration volume in the long dwell. In a Cochrane review, use of icodextrin appeared to improve fluid status in PD patients. However, most patients can be treated with nonhypertonic glucose solutions if their dwell time is adapted appropriately to their small-solute transport rate.

Restriction of salt and fluid intake is probably the most effective way to avoid fluid overload. In this regard, a strategy whereby dietary restriction of sodium and fluid intake are started early and combined with an individualized prescription of dwell time might prove to be worthwhile. As residual renal function decreases, icodextrin can be added to enhance ultrafiltration volume. The need for hypertonic exchanges should be delayed as long as possible to avoid more accelerated deterioration of the peritoneal membrane and residual renal function. Where available and affordable, low-GDP solutions might add to protection of residual renal function. Such a strategy currently is being tested in a large observational international trial of incident PD patients.

The most frustrating observation on fluid management in PD patients is that there are technical limits on what reasonably can be achieved with the technique. Adequate and timely preparation of the patient for an eventual transfer to hemodialysis therefore also should be part of a well-established program to maintain euvolemia.

REFERENCES


