Chapter 11
Secondary Causes: Work-Up and Its Specificities in CKD: Influence of Volume Overload, Excess Sodium Intake and Retention in CKD

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Worldwide, it is estimated that more than 1 billion adults have hypertension; its prevalence is projected to climb to 1.5 billion by the year 2025 [1]; it is associated with premature death, stroke, and heart disease. The pathogenesis of hypertension is complex, involving increased systemic vascular resistance, arterial stiffening, cardiac output, excess salt intake, fluid retention, or a combination of all of these factors. The kidney plays an essential role in blood pressure (BP) pathogenesis, by appropriate renal adjustments of sodium balance and blood volume.

New Pathological Mechanisms Beyond Guyton's Theory

According to the classic concept of Guyton, high salt intake expands circulatory volume, which leads to an increase in perfusion pressure of the kidneys and in natriuresis that tends to restore the increased circulating volume to normal [2]. This pressure-natriuresis mechanism prevents the increase in BP that could arise from transient increase of circulating volume. In the context of induced renal dysfunction in animal experiments or in patients with chronic kidney disease (CKD), sodium loading causes extracellular volume expansion and volume loaded hypertension.

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According to this hypothesis, hypertension can develop only when the excretory ability of the kidney is impaired; in this context, the *kidney plays an essential role in BP regulation*. Moreover, it has been shown that mutations in a large number of genes related to the salt transport in the kidney determine monogenic forms of hypertension [3]. Fujita et al. recently identified two important signaling pathways in renal tubules that play key roles in electrolyte balance and the maintenance of normal BP: the β2-adrenergic stimulant-glucocorticoid receptor (GR)-with-no-lysine kinase (WNK)4-Na(+)-Cl(−) cotransporter pathway, which is active in the distal convoluted tubule (DCT) 1, and the Ras-related C3 botulinum toxin substrate (Rac)1-mineralocorticoid receptor (MR) pathway, which is active in DCT 2, connecting tubules, and collecting ducts. β2-Adrenergic stimulation due to increased renal sympathetic activity in obesity- and salt-induced hypertension suppresses histone deacetylase 8 activity via cAMP/PKA signaling, increasing the accessibility of GRs to the negative GR response element in the WNK4 promoter. This results in the suppression of WNK4 transcription followed by the activation of Na(+)-Cl(−) cotransporters in the DCT and elevated Na(+) retention and BP upon salt loading. The authors suggested that these new pathways might be novel therapeutic targets for the treatment of salt-sensitive hypertension and new diagnostic tools for determining the salt sensitivity of hypertensive patients [4].

However, in the last 15 years, the Guyton's traditional view was contradicted. In an elegant study, Heer et al. found that high sodium intake increases plasma volume in a dose-dependent manner, but not total body water. They concluded that in contrast to the traditional view, high sodium intake does not induce total body water storage but induces a relative fluid shift from the interstitial into the intravascular space [5]. More recently, Tietze et al. demonstrated that considerable quantities of nonosmotic sodium are accumulated in various tissues, such as skin, cartilage, bone, and muscle without water retention [6].

Experimental studies have shown that negatively charged glycosaminoglycans (GAG) in the skin interstitium are responsible for sodium storage. In rats, excess dietary sodium has been linked with (1) increased interstitial GAG content, (2) increased polymerization and sulfation of these GAGs, and (3) increased skin sodium concentrations (180–190 mmol/L) which exceed plasma sodium concentrations and was not accompanied by extracellular water retention.

It seems that nonosmotic sodium accumulation, which occurs acutely, is followed by amplified removal from skin via the newly developed lymphatics for ultimate renal excretion. In rats, a high-salt diet leads to interstitial hypertonic sodium accumulation in skin [7], resulting in increased density and hyperplasia of the lymph and capillary network. The mechanisms underlying these effects on lymphatics involve activation of tonicity-responsive enhancer binding protein (TonEBP) in mononuclear phagocyte system (MPS) cells infiltrating the interstitium of the skin. TonEBP binds the promoter of the gene encoding vascular endothelial growth factor C (VEGF-C) and causes VEGF-C secretion by macrophages [8] (Fig. 11.1). As a consequence, increased density and hyperplasia of the skin lymphocapillary network and increased endothelial nitric oxide synthesis is observed. MPS cell depletion or VEGF-C trapping by soluble VEGF receptor-3 blocks VEGF-C signaling, augments interstitial hypertonic volume retention, decreases endothelial nitric oxide synthase expression, and elevates BP in response to high-salt diet. The MPS cells act as onsite controllers of interstitial

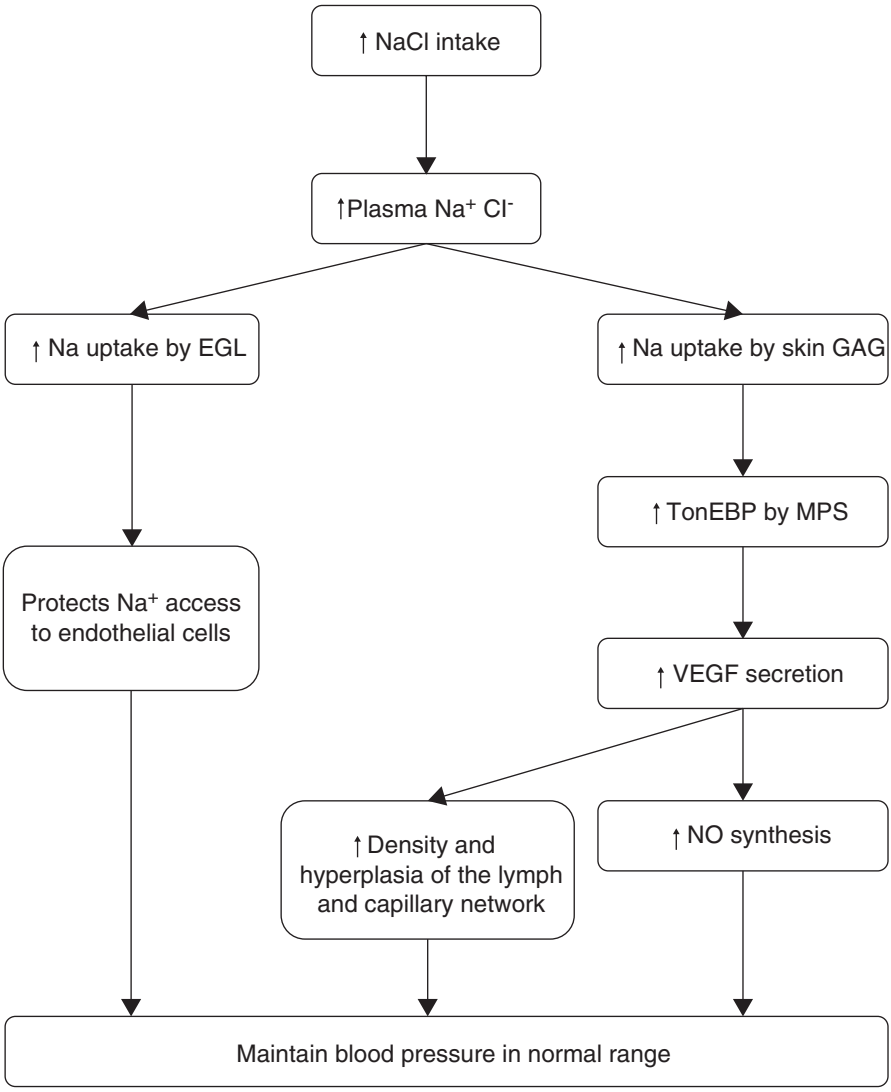

Fig. 11.1 Potential defensive mechanisms for high salt intake. *EGL* endothelial glycocalyx layer, *GAG* glycosaminoglycans, *MPS* mononuclear phagocyte system, *NO* nitric oxide, *TonEBP* tonicity-responsive enhancer binding protein, *VEGF* vascular endothelial growth factor

volume and BP homeostasis, providing a local regulatory salt-sensitive tonicity-responsive enhancer binding protein/vascular endothelial growth factor C-mediated mechanism in the skin to maintain normal blood pressure in states of interstitial Na(+) and Cl(−) accumulation. Failure of this physiological extrarenal regulatory mechanism leads to a salt-sensitive blood pressure response [7].

Another important player in this concept is the endothelial surface layer, a dynamic layer on the luminal side of the endothelium that is in continuous exchange with flowing blood. This soft surface layer, named endothelial glycocalyx layer

(EGL), is a negatively charged biopolymer known to preferentially bind sodium, because negatively charged GAG are abundantly present in this layer. Additionally, it is involved in regulating vascular permeability, has antiatherogenic and anti-inflammatory properties, and is an important mediator in shear-induced nitric oxide (NO) production.

At present, the sodium binding capacity of the EGL is not known. However, the sodium excess determines a reduction of heparin sulfate residues by 68%, which leads to destabilization and collapse of the EGL. Subsequently, sodium is bringing into the endothelial cells. Sodium overload transformed the endothelial cells from a sodium release into a sodium-absorbing state. These results might elucidate endothelial dysfunction and arterial hypertension associated with sodium abuse [9].

Additionally, in some pathological situation such as severe sepsis, CKD, or end-stage renal disease (ESRD), or during acute or chronic hyperglycemia, the EGL is perturbed, which is accompanied by an expanded extracellular volume, higher BP, or both, suggesting that variability in sodium homeostasis and salt sensitivity may be related to the quality of the EGL, in which endothelial GAGs act as an intravascular buffer compartment for sodium. For example, in 23 stable dialysis patients, the EGL alteration was associated with an increased need for ultrafiltration.

Endothelial surface layer has also been reported to influence the availability of NO production via mediating the epithelial sodium channel on the endothelial luminal surface (EnNaC). When the plasma sodium was increased, the density of EnNaC has been shown to be increased to leading to increasing sodium uptake, stiffen the endothelial cellular cortex, and diminishing NO production. Taken together, an increase of sodium delivery to the endothelial cell resulted in an increase in vascular tone [10].

Salt and Hypertension in the General Population

Alteration in dietary sodium determines different BP responses; if BP increases during a period of high dietary sodium or declines during a period of low sodium, these individuals have salt-sensitive hypertension. If there is no change in BP with sodium restriction, that individual has salt-resistant hypertension. Salt sensitivity in normotensives is associated with future hypertension; salt sensitivity hypertension is associated with increased mortality.

Salt sensitivity has been shown to be mainly prevalent in black, in obese, and in elderly hypertensive patients. It is frequently associated with diminished renal function and by a significantly enhanced cardiovascular risk. Furthermore, it is also associated with microalbuminuria, absence of the nocturnal decrease in arterial pressure, and absence of modulation of renal blood flow in response to sodium loading.

Excess salt intake is one of the most common and important risk factors involved in the pathogenesis of hypertension. Numerous animal studies [11–13] and clinical trials found a causal relation between salt intake and hypertension [14–19].

Additionally, data from epidemiological studies have shown a direct and positive association between excess salt intake and cardiovascular disease.

The INTERSALT Study engaged a standardized protocol with careful attention to the measurement of BP and collection of "gold standard" 24-h urinary Na estimates in 10,079 adults from 32 countries, providing a wide range in Na (the exposure variable). A significant positive relationship was shown between dietary Na and BP for both within- and across-population analyses. Recently, the Prospective Urban Rural Epidemiology (PURE) study provided new evidence about the association between sodium and potassium intake, estimated from morning urine specimens, BP, death, and major cardiovascular events [20]. In this study of 102,216 adults from 18 countries and 5 continents, the authors found a positive but heterogeneous association between estimated sodium excretion and BP. Approximately 90% of the participants had either a high (>5.99 g per day) or moderate (3.00–5.99 g per day) level of sodium excretion; approximately 10% excreted less than 3.00 g per day, and only 4% had sodium excretion in the range associated with current US guidelines for sodium intake (2.3 or 1.5 g per day). The authors found a steeper slope for this association among study participants with sodium excretion of more than 5 g per day, a modest association among those with sodium excretion of 3–5 g per day, and no significant association among those with sodium excretion of less than 3 g per day. The authors concluded from the findings that a very small proportion of the worldwide population consumes a low-sodium diet and that sodium intake is not related to BP in these persons, calling into question the feasibility and usefulness of reducing dietary sodium as a population-based strategy for reducing BP [20, 21]. Another very important finding of this study is the relation between sodium excretion and potassium excretion in regard to BP: high sodium excretion was more powerfully associated with increased BP in persons with lower potassium excretion; they proposed that the alternative approach of recommending high-quality diets rich in potassium might achieve greater health benefits, including blood pressure reduction, than aggressive sodium reduction alone. The major limitations of this study are (1) the absence of the direct measurements on 24-h urinary excretion on numerous occasions, which is the accepted model for evaluating electrolyte intake, and (2) the lack of an intervention component to assess the direct effects of altering sodium and potassium intake on blood pressure, thus making it unfeasible to establish causality.

On the other hand, sodium restriction determines a significant reduction in BP, with multiple meta-analysis and systematic reviews of randomized controlled trials showing this effect. The last one, published last year, from the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCode) including 107 randomized interventions in 103 trials, showed a linear dose–response relationship between reduced sodium intake and BP, jointly modified according to age, race, and the presence or absence of hypertension. The authors explained that larger effects in older adults and hypertensive persons would be consistent with decreasing vascular compliance and renal filtration; in blacks, larger effects would be consistent with differences in renal handling of sodium [22].

Salt and Hypertension in CKD

Evidence shows that almost all CKD patients are salt sensitive; in these patients, high salt intake is linked to risk factors for both heart disease and worsening kidney function, including high BP, excess proteinuria, and fluid overload. The effect of sodium intake on BP is traditionally thought to be driven primarily through changes in fluid volume, mediated by the renin-angiotensin-aldosterone system (RAAS), although recent research indicates that other mediators, like vascular stiffness or inflammation, may play an important role.

High sodium intake is thought to have direct toxic effects on blood vessels through mediating factors such as oxidative stress, inflammation, endothelial cell dysfunction, and vascular stiffness. High sodium intake enhances the generation of superoxide anion accompanied by enhanced renal expression and nicotinamide dehydrogenase activation. In addition, dietary salt increases the glomerular expression of TGF-β1 on renal tissue and also augments nitric oxide production. High salt intake also induces the intrarenal aldosterone receptor and promotes renal fibrotic injury; it might also determine tissue inflammation by triggering IL-17-producing CD4+ T cell development [23].

Moreover, the excess sodium intake abrogates the antiproteinuric effects of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), thereby exacerbating proteinuria. Sodium restriction amplifies the top of the dose response of RAAS-blockade for both blood pressure and proteinuria. The effect of moderate sodium restriction during RAAS-blockade on blood pressure and proteinuria is almost similar to the effect of adding a diuretic. In a recent systematic review and meta-analysis, including 11 studies and 516 participants, sodium intake reduction markedly reduces albumin excretion, more so during concomitant RAAS-blocking therapy and among patients with kidney damage. An average reduction in sodium intake of 92 mmol/d was associated with a 32.1% reduction in urinary albumin excretion. A greater reduction of urinary albumin excretion was associated with a higher decrease in BP during the intervention [24].

There were several short-term studies on the effect of restricting salt intake on BP levels in CKD patients. In a small prospective trial of patients with CKD, McMahon and colleagues determined that a low-sodium diet (60–80 mmol/d) resulted in a reduction of 10 mmHg systolic pressure compared with a high-sodium diet. The authors also demonstrated that the low-sodium diet in this trial reduced protein excretion by more than 300 mg/d and also the extracellular volume [25, 26]. In a recent Cochrane meta-analysis including 8 studies and 258 people (with early-stage CKD, renal transplantation, one study, and peritoneal dialysis, one study), reduced sodium intake significantly reduced BP and antihypertensive medication dosage [27]. However, the authors found a critical evidence gap in long-term effects of salt restriction in people with CKD; they were unable to determine the direct effects of sodium restriction on primary endpoints such as mortality and progression to ESRD.

Volume Overload and Hypertension

It is now recognized that unidentified, clinically unapparent volume expansion is an important cause for hypertension and resistance to antihypertensive treatment [28]. Several methods have been used for optimal determination of volemia, including clinical examination, measurement of inferior cave vein diameter using echocardiography, and the evaluation of cardiac biomarkers—mainly N-terminal prohormone brain natriuretic peptide (NT proBNP) or impedance measurements.

A positive correlation between measured plasma volume and systolic and diastolic BP was shown in several studies [29]; additionally, intensified diuretic treatment improved BP control via a quantifiable decrease in plasma volume [30, 31]. In the last 15 years, thoracic bioimpedance was used to evaluate hemodynamic status and to adjust complex antihypertensive treatment in general population. Taler et al. in a series of 104 patients with resistant hypertension randomized to hemodynamic guided treatment or specialist care showed that the patients treated according to hemodynamic measurements had an improved BP control rate (56% versus 33% in the control group, $P < 0.05$) and incremental reduction in systemic vascular resistance measurements compared with the group of patients treated as per clinical judgment alone. Higher doses of diuretics (not a greater prevalence of use) were prescribed for the hemodynamically managed group, leading to a greater blood pressure lowering [32]. Smith et al. investigated the role of hypertension therapy guided by impedance in 164 patients with uncontrolled hypertension and no significant accompanying diseases [33]. After 3 months of treatment, therapy based on hemodynamic evaluation was associated with considerably better BP control, including a significant decrease in average systolic and diastolic BP values. The hemodynamic arm achieved the BP goal (<140/90 mmHg) more frequently (77% versus 57% $P < 0.01$ and 55% versus 27% for a more aggressive BP control – at <130/85 mmHg $P < 0.0001$) compared with the control group. Similar results were obtained by Krzesinski et al. in 128 patients with uncontrolled hypertension [34]. Therapy based on impedance cardiography significantly increased the reduction in office systolic BP (11.0 vs. 17.3 mmHg; $p = 0.008$) and diastolic pressure (7.7 vs. 12.2 mmHg; $p = 0.0008$), as well as 24-h mean systolic BP (9.8 vs. 14.2 mmHg; $p = 0.026$), daytime systolic BP (10.5 vs. 14.8 mmHg; $p = 0.040$), and night-time systolic BP (7.7 vs. 12.2 mmHg; $p = 0.032$) [35].

Subclinical volume overload is present in more than 20% of CKD patients. In a prospective cohort study including 338 patients with CKD stage 3–5, fluid overload was associated with BP, proteinuria, renal inflammation with macrophage infiltration and tumor necrosis factor-α overexpression, glomerular sclerosis, and cardiac fibrosis [36]. Hung et al. used the body composition monitor, a multifrequency bioimpedance device, to measure the level of overhydration in CKD patients. Of the 338 patients with stages 3–5 CKD, included in this study, only 48% were euvolemic. Patients with volume overload were found to use significantly more antihypertensive medications and diuretics but had higher systolic BP and an increased arterial stiffness than patients without volume overload [37].

The value of guiding hypertension treatment based on subclinical extracellular fluid excess has been tested in one pilot study. Verdalles et al. used bioimpedance to assess fluid status and to guide diuretic therapy for treating hypertension in CKD patients [38]. They treated 30 patients with extracellular volume (ECV) expansion with a diuretic in contrast to 20 patients without ECV expansion who as an alternative received another additional antihypertensive medication. At 6 months of follow-up, systolic BP decreased by 21 mmHg in patients with expansion of ECV compared with 9 mmHg in patients without expansion of ECV ($P < 0.01$). In addition, nine of 30 patients with ECV expansion and two of 20 without ECV expansion achieved the target blood pressure of less than 140/90 mmHg at 6 months.

In hemodialysis, approximately 25% of the patients are overhydrated; based on bioimpedance and BP measurements, Wabel et al. described four distinct categories of individuals in dialysis: (i) normotensive, normovolemics; (ii) hypertensive, normovolemics; (iii) hypertensive, hypervolemics; and (iv) normotensive, hypervolemics. It is obvious that BP management by different classes of drugs could be tailored much easier and related to prevailing underlying pathophysiological mechanisms [39].

Furthermore, the impact of volume overload correction on BP management has been tested in several studies. In the DRIP study, Agarwal et al. included 150 patients without obvious volume overload; 50 patients were randomized to a control group and 100 patients randomized to ultrafiltration group, and all underwent interdialytic ambulatory BP monitoring three times (at baseline, 4 weeks, and 8 weeks). In the ultrafiltration group, the ambulatory BP was reduced within 4 weeks by 7/3 mmHg. This antihypertensive effect was sustained for 8 weeks of observation. Despite provoking occasional uncomfortable intradialytic symptoms, the quality of life was not impaired with reducing dry weight [40].

Additionally, bioimpedance-guided fluid management was associated with an improvement in BP control, intradialytic symptoms, left ventricular mass index, or arterial stiffness. Moissl et al. optimized the fluid status of 55 HD patients using a bioimpedance device over the course of 3 months. This active fluid management improved significantly the BP control; every 1 l change in fluid overload was accompanied by a 9.9 mmHg/L change in predialysis systolic BP [41].

Similar results were reported by Hur et al. in a prospective randomized trial including 156 hemodialysis patients; in the interventional group ($n = 78$), the fluid management was guided using bioimpedance; in the control group ($n = 78$), the fluid removal during dialysis was determined according to usual clinical practice. Pre- and post-dialysis systolic and diastolic BP significantly decreased in the intervention group compared with the control group. Moreover, a significant reduction in the left ventricular mass index was also observed in the intervention group as compared with the control group (mean difference between groups: −10.2; 95% CI −19.2 to −1.17; $p = 0.04$) [42]. Moreover, in another randomized trial, Onofriescu et al. showed that strict volume control guide by bioimpedance is associated with better survival rate ($P = 0.03$). After 2.5 years there was also an improvement arterial stiffness (measured with pulse wave velocity [m/s]) was significantly higher in the intervention group (−1.50 compared with 1.2; mean difference in change: −2.78; 95% CI −3.75 to 1.80; $p < 0.001$) [43].

In contrast, Ponce et al. founded that volume control was not associated with better BP control in 189 hemodialysis patients from 23 dialysis centers, although bioimpedance measurements provided a better volume control, BP, the number of hypotensive events, and hospitalizations were similar between the two groups [44].

Hypertension is also common in peritoneal dialysis; the presence of latent hypervolemia or insufficient patient compliance to salt and fluid retention might have a major role. Results of the recently published European Body Composition study showed that fluid overload is a frequent problem in this group of patients (severe fluid overload was present in 25.2% of 639 PD patients) [45]. Chen et al., in a prospective study including 121 HD and 84 PD patients, observed that all patients with overhydration had hypertension in both the hemodialysis and peritoneal dialysis groups [46]. Yilmaz et al. investigated the association between hydration status, measured with BIA methods and BP and left ventricular mass index (LVMI) in 43 HD and 33 PD patients. Systolic BP in both post-HD and PD groups and LVMI in the PD group were found to be significantly higher in overhydrated patients. In multiple linear regression analyses, fluid overload was independently associated with higher systolic BP and LVMI [47].

The impact of strict volume control on BP, LVMI, or mortality was evaluated in several studies. In 47 hypertensive PD patients, antihypertensive medications were discontinued, and salt restriction was initiated. In patients with persistent elevation of BP, enhanced peritoneal ultrafiltration was implemented by the use of a hypertonic dialysis solution (4.25% dextrose). Salt restriction alone or combined with ultrafiltration led to a decline in body weight by a mean of 2.8 kg, and BP decreased from a mean of 158.2 ± 17.0/95.7 ± 10.3 to 119.7 ± 16.0/779 ± 9.7 mmHg. Additionally, a significant decrease of the cardiothoracic index on the chest radiograph was also noted: from 48.0% ± 5.6% to 42.9% ± 4.5% [48].

In a randomized controlled study, Tang et al. used bioimpedance to improve the volume control and BP in 160 PD patients. The patients were randomly allocated to 2 groups: in Group 1 the patients and their primary nurses were informed of the overhydration values provided by bioimpedance spectroscopy, whereas in Group 2 the values were not revealed, and patients' volume was measured by the standard methods; the use of bioimpedance was associated with a better volume control and a significant improvement in systolic BP [49].

Another bedside method that received growing attention in recent years is lung ultrasonography (LUS) (Fig. 11.2). It determines the extravascular lung water, a small, but important component of total body fluids that represents the water content of lung interstitium and is strictly dependent on the filling pressure of the left ventricle. The comet-tail artifacts, also known as B-lines, are a type of reverberation phenomenon that occurs as a consequence of the mismatch between edematous septa and the overlying pleura [50, 51].

Although B-lines are a reliable diagnostic tool for the assessment and staging of the pulmonary congestion in heart failure patients, this method could be also of help in managing hypertension, especially in CKD patients. Several studies found a significant association between B-lines score and BP [52–55], but only in the simple correlation analysis. There was also observed an association between the B-lines score and bioimpedance parameters in some [57] but not all studies [52, 58].

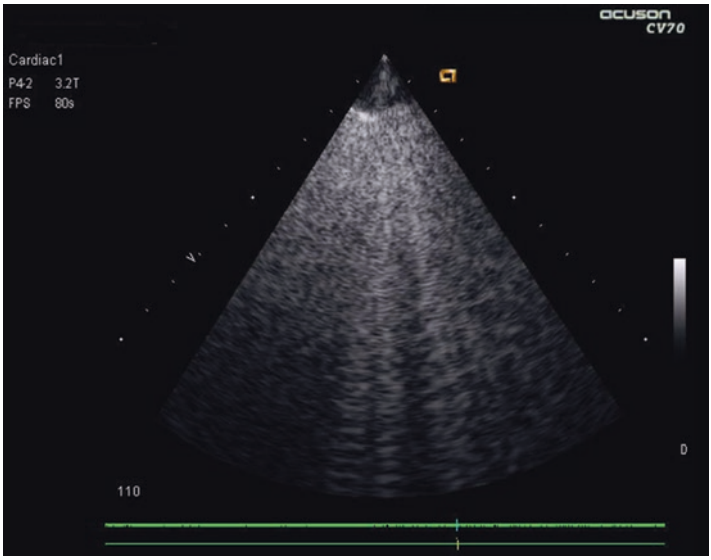

Fig. 11.2 B-lines by lung ultrasonography

In hemodialysis patients, the B-line score is associated with cardiovascular events [54] and all-cause mortality [54, 56, 59]. However, Siriopol et al. showed that only bioimpedance, and not lung ultrasonography, improves risk prediction for death, beyond classical and echocardiographic-based risk prediction scores/parameters [59]. Bioimpedance and lung ultrasonography may be complementary, providing different information, with bioimpedance being more specific to fluid status and lung ultrasonography to cardiac function. Although bioimpedance seems to possess more prognostic capabilities, in specific patients, a dry weight estimation based on lung ultrasonography could be considered. Currently, two randomized controlled trials regarding this approach are ongoing (ClinicalTrials.gov Identifiers: NCT01815762 and NCT02310061).

Conclusions

In conclusion, salt and volume matters. Maybe it is time to use individualized hemodynamic measures and individualized antihypertensive treatment in all patients. Although we have numerous drugs to lower BP, we have never aligned how we think they work with any phenotyping (or genotyping). So we have a "one size fits all" approach to raised BP. In CKD, we can see the folly of this all too clearly. Salt and water could make the difference. Given that we can now measure volume expansion reliably and noninvasively, and titrate BP treatment, why do we not bother, in all patients?

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