ACID-BASE AND ELECTROLYTE ABNORMALITIES OBSERVED IN PATIENTS RECEIVING CARDIOVASCULAR DRUGS

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ABSTRACT

Cardiovascular drugs can cause a variety of acid-base and electrolyte abnormalities, which need to be considered when managing the large number of patients receiving these agents. Diuretic-induced metabolic alkalosis is the most common acid-base disorder observed and is associated with hypokalemia. Drug-induced hyperkalemia is the most important cause of increased potassium levels in the everyday clinical practice. Multifactorial origin diuretic-induced hyponatremia is mostly due to thiazides and should be carefully managed.

In this review, we focused on the pathogenetic mechanisms as well as on the treatment of these metabolic derangements commonly encountered in patients receiving cardiovascular drugs.

Key words: Acid-base abnormalities, electrolyte disorders, cardiovascular drugs, metabolic alkalosis, hypokalemia, drug-induced hyperkalemia, hyponatremia
INTRODUCTION

Cardiovascular drugs are among the most frequently prescribed medications. However, they can cause a number of acid-base and electrolyte disturbances that may complicate treatment with these drugs. Knowledge of these adverse metabolic effects can help clinicians identify and treat at risk patients. In this review we describe these acid-base and electrolyte abnormalities as well as their pathogenesis and treatment.
1. DIURETICS

1A. Loop and thiazide-type diuretics

Metabolic alkalosis is fairly common after the administration of loop and thiazide-type diuretics. The severity of alkalemia varies directly with the degree of diuresis. Metabolic alkalosis is related to the coexistent contraction of the extracellular volume around a constant amount of extracellular $\text{HCO}_3^-$ (contraction alkalosis) as well as to increased urinary $\text{H}^+$ loss ascribed to enhanced distal $\text{H}^+$ secretion [1,2]. The latter is primarily due to volume depletion-induced hypersecretion of aldosterone and the diuretic-induced concomitant potassium depletion [3]. Both hypovolemia and hypokalemia are particularly important for the perpetuation of alkalemia, since they promote renal $\text{HCO}_3^-$ reabsorption, thus impeding the excretion of excess $\text{HCO}_3^-$ [4]. In these cases the increase in $\text{HCO}_3^-$ reabsorption that maintains the alkalosis can be reversed by the correction of hypovolemia and hypokalemia (e.g. half-isotonic saline plus potassium chloride) [5]. In edematous patients the administration of saline solutions is not indicated; in such cases the administration of acetazolamide (a carbonic anhydrase inhibitor that increases the renal excretion of $\text{NaHCO}_3$) is particularly useful in treating both alkalemia and edema [6]. However, drug treatment is usually followed by the development or the deterioration of hypokalemia [6]. Acetazolamide can also be used in patients with cor pulmonale and chronic hypercapnia, because in this setting the correction of alkalemia is mandatory, since it can further depress ventilation [7,8]. However, the drug can impair carbon dioxide elimination in patients with chronic obstructive lung disease and therefore should be used with great caution [9]. In severe cases HCl can be given to lower $\text{HCO}_3^-$ concentration as an isotonic solution infused into a major vein [10].

Recent data have shown that metabolic alkalosis can diminish natriuresis to loop diuretics and therefore it should be corrected in diuretic-resistant subjects [11].
Hypokalemia is the most common and important side-effect of both loop and thiazide-type diuretics and is related to increased potassium excretion [3,12,13]. The incidence of the decreased potassium levels is dose-related as well as drug-related. In fact, chlorthalidone, a long-acting drug, has a greater kaliuretic effect compared to other thiazides [14,15]. Indapamide is also followed by a significant decrease in serum potassium levels [16]. Even though loop diuretics are more potent, they tend to produce less hypokalemia compared to thiazides. It has been suggested that changes in calcium handling may explain this difference between the two classes of diuretics. Loop diuretics decrease calcium reabsorption in the loop of Henle thus increasing the distal calcium delivery. Experimental data have shown that luminal calcium can regulate (decrease) potassium transport by the renal distal tubules, perhaps by impairing sodium reabsorption at this site [15,17]. A number of factors are responsible for the potassium deficit observed in patients on diuretics. 1) The hypovolemia or the underlying disease (such as congestive heart failure)-induced secondary aldosteronism, 2) The increased flow to the distal secretory sites, due to inhibition of sodium chloride and water reabsorption in the loop of Henle or distal tubules, 3) The coexistent diuretic-induced hypomagnesemia, which can lead to potassium depletion due to both urinary and fecal losses, and 4) The decreased potassium reabsorption by the \( \text{Na}^+\text{-K}^+\text{-2Cl}^- \) carrier in the loop of Henle (in cases of loop diuretics) [3,12,13].

Hypokalemia may lead to potentially deleterious cardiac arrhythmias, especially in hypertensive patients with left ventricular hypertrophy (LVH), as well as in patients with heart failure, coronary ischemia, and concomitant digitalis therapy [15, 18-20]. In fact, digitalis-induced arrhythmias can be observed even if its plasma levels are within normal limits when hypokalemia is present [21]. Analysis of the results of the Multiple Risk Factors Intervention Trials (MRFIT) and other studies suggest that antihypertensive treatment may be associated with an increased risk of sudden cardiac death possibly related to the
diuretic-induced electrolyte abnormalities [22,23]. Analysis of the Framingham Heart Study showed that the risk of cardiac arrhythmias (complex or frequent ventricular beats) increased by 27% with each 0.5 mmol/L reduction in serum K⁺ concentration [20]. Moreover, the acute coronary ischemia stress-induced release of epinephrine can promote K⁺ entry into cells and can further worsen the hypokalemia with devastating consequences [18-20].

It should be mentioned that electrolyte abnormalities, such as hypokalemia and hypomagnesemia, are important risk factors for the development of polymorphic ventricular tachycardia and torsade de pointes in patients also treated with drugs that prolong the QT interval [21]. Finally, potassium depletion can increase blood pressure by a mean of 5 to 7 mmHg partly due to sodium retention and the incidence of stroke, independently of other cardiovascular risk factors [21].

However, it has recently been emphasized that hypokalemia is not a significant problem in hypertensive patients treated with relatively small doses of thiazides (e.g. 12.5 mg of hydrochlorothiazide or its equivalent). Interestingly, these doses can produce an antihypertensive effect similar to that of higher doses but with limited metabolic side-effects [22-27]. Notwithstanding, a recent analysis of the SHEP trial showed that the participants who experienced hypokalemia after one year of treatment with a low-dose diuretic did not experience the reduction in cardiovascular events achieved among those who did not have hypokalemia [28].

Finally, it is worth mentioning that the diuretic-induced potassium deficit is usually noted during the first weeks of treatment. Thus, if the diuretic dose and dietary intake remain constant and there is no other abnormality in potassium balance, a new steady state is reached in which K⁺ intake and output are again equal. The diuretic-induced kaliuria is counterbalanced by the associated hypovolemia-induced decrease in distal flow and direct potassium sparing effect of hypokalemia. Thus, a patient with normal serum potassium
levels at 3-4 weeks after drug administration is not at risk for developing late hypokalemia, unless another disturbance of potassium homeostasis is superimposed [13]. In cases of diuretic-induced hypokalemia, it should be carefully treated with potassium chloride supplements or with potassium-sparing diuretics [29-35]. These drugs can also partially correct diuretic-induced magnesium depletion by diminishing magnesium excretion. This effect may be particularly important in patients who also exhibit abnormalities of magnesium homeostasis, which can also be arrhythmogenic [30]. In addition, the correction of hypokalemia in hypertensive patients can produce a small further decrease in blood pressure (by an average of 6/3 mmHg) [34].

Mild hyponatremia is commonly found in patients taking diuretics. However, acute severe hyponatremia is occasionally observed as an idiosyncratic reaction [36-41], particularly in patients who consume large quantities of water [38-42]. Interestingly, diuretic-induced hyponatremia is mostly due to thiazides and not to loop diuretics. This finding is related to the different sites of action of these drugs within the nephron. Thus, loop diuretics interfere with urinary concentration and subsequently with the ADH-induced free-water reabsorption in the collecting tubules. On the other hand, thiazides acting in the distal tubules do not interfere with the urinary concentration and the ability of ADH to promote water retention, which is the critical point for the development of hyponatremia [36-42]. It should be mentioned that indapamide as well as the hydrochlorothiazide plus amiloride combination are also followed by hyponatremia. In fact, a recent report has shown that there was a greater incidence of hyponatremia with the hydrochlorothiazide and amiloride combination than with hydrochlorothiazide alone [16]. A number of interrelated mechanisms contribute to the development of hyponatremia after diuretic administration; a) excess renal loss of effective osmoles (K\(^+\)+Na\(^+\)) compared to water losses due both to diuretic-induced electrolyte losses and ADH-induced water retention [39], b) diuretic-induced volume depletion leading to appropriate ADH hypersecretion, c)
the coexistent hypokalemia, which results in a transcellular cation exchange ($\text{Na}^+$ moves into the cells while potassium exit to preserve electroneutrality), d) direct inhibition of urinary dilution by diminishing $\text{NaCl}$ reabsorption in the renal tubules [41], e) increased water intake, as previously described [38], f) a syndrome of inappropriate secretion of ADH (SIADH) has also been implicated as a cause of hyponatremia. In fact, in a considerable number of patients with thiazide-induced hyponatremia there are findings suggestive of volume expansion, such as low values of blood urea nitrogen (BUN) and uric acid levels with increased fractional excretion of these parameters [43]. In contrast, when hypovolemia is the primary underlying mechanism, increased serum urea and uric acid levels are found [43,44]. It should be mentioned that as happens with most of the metabolic side effects of diuretics, hyponatremia occurs within 2 weeks of the start of therapy. In fact, after the first weeks of treatment, a new steady state is established in which intake and excretion are again equal. Any further decrease in serum sodium is found only in cases of a superimposed abnormality of water homeostasis due to additional volume losses, decrease in renal function, increase in the dose of the drug or in fluid intake, etc [41,45].

Diuretic-induced hyponatremia can be managed by restricting the dietary intake of free water, restoring potassium losses and reducing the dose of thiazides or withdrawing the diuretic. Severe symptomatic hyponatremia should be carefully corrected with the combination of saline and potassium solutions. In such cases the risks of ongoing hyponatremia must be balanced against those of a rapid correction. Thus, the serum sodium should be reduced by less than 10-12 mmol/L on the first day and by less than 18 mmol/L over the first two days of treatment [46,47].

Loop diuretics impair urinary concentration resulting in increased hypotonic losses and elevated sodium levels. However, these drugs are short-acting and the water losses can
be easily replaced by oral intake. Thus, hypernatremia is not usually found in these cases unless access to free water is limited [48].

Magnesium depletion and/or hypomagnesemia are relatively common after using diuretics [49-51]. However, the plasma magnesium concentration often remains within or near the normal range, while it has been suggested that most of the magnesium losses derive from the cells [30,52].

The cortical aspect of the thick ascending limb of loop of Henle is the main site of magnesium reabsorption (50-60%) [52]. As it is well known the reabsorption of sodium chloride via the $\text{K}^+-\text{Na}^+-2\text{Cl}^-$ cotransporter, in combination with a $\text{K}^+$-leak at the luminal membrane, creates an electrical gradient (with the lumen relatively electropositive) which promotes the passive paracellular (between cells) reabsorption of divalent cations, such as magnesium and calcium [53]. Loop diuretics decrease sodium chloride reabsorption in the loop of Henle by competing for the chloride site on the $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ contransporter thus impeding the electrical gradient that promotes the passive paracellular reabsorption of divalent cations, leading to increased magnesium (and calcium) excretion and hypomagnesemia [53,54].

Distal magnesium reabsorption primarily occurs in the cortical collecting tubules. Magnesium enters into tubular cells through channels in the luminal membrane, a process which is enhanced by the favorable electrochemical gradient across the luminal membrane. Next, the reabsorbed magnesium passes through the basolateral membrane to the peritubular capillary, a process which involves sodium-magnesium exchange and is mediated by the low sodium concentration within the cell ($\approx 10-15 \text{ mmol/L}$) compared to that in the extracellular volume [52], which favors sodium entry into cells and the subsequent exit of magnesium.

The effect of thiazide diuretics on magnesium reabsorption depends on the type of administration. The acute administration of thiazides inhibits the entry of sodium chloride
into cells [55], thereby increasing magnesium reabsorption, which is driven by the favorable electrochemical gradient across the lumen, which is inversely related to sodium reabsorption [56]. However, chronic administration of thiazides can increase magnesium excretion due to coexistent potassium depletion, which directly inhibits distal tubular cell magnesium reabsorption as well as to hypovolemia-induced secondary aldosteronism [49,50,57]. In fact, aldosterone may enhance magnesium excretion, since it can increase the number of open luminal sodium channels and Na⁺ reabsorption and raise cell Na⁺ concentration in the cortical collecting tubules, thereby decreasing the gradient for Na⁺ entry across the basolateral membrane and subsequently the degree of Mg exit towards the peritubular capillary [57]. In support to this suggestion the potassium sparing diuretics, which decrease the aldosterone effects on collecting tubules, can decrease magnesium excretion [30,58]. It should be mentioned that magnesium depletion may play an important role in the development of cardiac arrhythmias, especially in patients who also exhibit hypokalemia [49,59,60]. Thus, magnesium deficit should be treated with magnesium preparations, while potassium sparing diuretics, which limit both potassium or magnesium losses may be preferable in cases of diuretic-induced electrolyte derangements [49,59,60].

Filtered calcium is reabsorbed passively in the proximal tubules as well as in the loop of Henle down the favorable electrochemical gradient generated by sodium (and water) reabsorption in combination with a K⁺-leak at the luminal membrane. In the distal tubules calcium transport is regulated by the level of calcium balance and is influenced by a number of hormones, such as parathyroid hormone (PTH) and calcitriol [61-63]. Both loop diuretics and thiazides can affect calcium balance and influence calcium levels [48]. Loop diuretics decrease sodium chloride transport in the loop of Henle, thereby inhibiting the generation of the electric gradient (with the lumen relatively electropositive), which is necessary for the passive paracellular reabsorption of calcium and magnesium. As a
result, furosemide can increase calcium excretion, making this drug useful for the treatment of hypercalcemia [48,64].

On the other hand, thiazides inhibit \( \text{Na}^+\text{-Cl}^- \) cotransporters in the luminal membrane of the distal tubules and thus decrease sodium chloride reabsorption. This natriuresis is followed by a significant decrease in calcium excretion [65] possibly due to the associated volume depletion, which augments proximal sodium chloride and simultaneously passive calcium reabsorption in this segment. Moreover, an active calcium transport in the distal tubules has also been suggested to play a role [66-69]. This hypocalciuric effect may be responsible for the improvement of calcium balance and the observed reduction in the incidence of hip fractures noticed after long-term thiazide administration [65,70]. A recent meta-analysis showed a 20% reduction in fractures after long-term thiazide administration [71]. Furthermore, this decreased calcium excretion may reduce the frequency of nephrolithiasis in patients with idiopathic hypercalciuria [13]. Thiazide diuretics evoke a small increase in serum calcium concentration [64], which is limited by the hypercalcemia-induced suppression of PTH secretion. However, in a few patients significant increases in serum calcium levels can be found. In such cases, the coexistent hemoconcentration may contribute to the development of hypercalcemia, since it may raise the plasma albumin concentration and thus the physiologically inactive concentration of albumin-bound calcium [72]. Notably, thiazides can cause hypercalcemia in anephric patients suggesting a bone effect as well [73].

Various diuretics can increase urinary phosphorus losses. Loop diuretics have minimal effects on phosphate excretion, since these drugs act on the loop of Henle where phosphate reabsorption is minimal. However, these drugs also exhibit a weak carbonic anhydrase activity, which can explain their weak phosphaturic effect. Thiazide diuretics also have weak phosphaturic effect, which is related to their inhibition of carbonic anhydrase [74].
1B. Potassium sparing diuretics

A mild hyperchloremic metabolic acidosis along with hyperkalemia is usually observed after the use of potassium sparing diuretics due to the lack of the aldosterone effect on H\(^+\) secretion [75-77]. It is noteworthy that hyperkalemia plays an important role in the development of metabolic acidosis, since it impairs NH\(_4\)+ production and excretion [78]. Generally, metabolic acidosis is usually mild with serum bicarbonate concentration > 15 mmol/L and can be controlled by the combination of a low potassium diet and small doses of furosemide (frusemide) resulting in increased distal sodium delivery and subsequently in enhanced K\(^+\) and H\(^+\) secretion [79].

Drug-induced hyperkalemia is the most important cause of increased potassium levels in clinical practice [80,81]. Among the drugs affecting potassium homeostasis potassium sparing diuretics, such as amiloride, triamterene and spironolactone, can precipitate hyperkalemia in some patients [80,81]. Patients with preexisting renal insufficiency, diabetes mellitus, or consuming other drugs that also impair potassium excretion (such as angiotensin converting enzyme inhibitors) appear to be more likely to develop hyperkalemia when treated with potassium sparing diuretics [76,82,83]. In a retrospective study, 5 patients exhibited severe hyperkalemia (serum potassium 9.4 to 11mEq/L) within 8 to 18 days of combination treatment with amiloride /hydrochlorothiazide (MODURETIC) and an angiotensin converting enzyme inhibitor [84]. It should be mentioned that significant hyperkalemia after spironolactone administration (300 mg/day) has been observed in hemodialysis patients, suggesting that aldosterone can also affect the cellular handling of potassium or its gastrointestinal excretion [85].

It should be mentioned that a mild hyponatremia is observed in patients with drug-induced hypoaldosteronism (for example in patients receiving amiloride, trimethoprim etc.) and is related to ongoing sodium losses leading to hypovolemia and increased ADH secretion [86]. Finally, potassium sparing diuretics, such as amiloride, which block sodium
entry into cells by closing luminal sodium channels, also increase calcium reabsorption in the distal nephron [66,69].

1C. Carbonic anydrase inhibitors

These drugs significantly decrease bicarbonate reabsorption in the proximal tubules. Thus, metabolic acidosis is commonly found in patients receiving carbonic anydrase inhibitors [21]. Acetazolamide is the most effective phosphaturic diuretic and this can be attributed to the fact that phosphorus reabsorption mainly occurs in the proximal tubules.

2. ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors reduce conversion of angiotensin I to angiotensin II in the circulation and perhaps also in the adrenal zona glomerulosa [87] and decrease both angiotensin II and potassium-mediated aldosterone release [87,88]. These drugs may also impair potassium excretion by reducing the glomerular filtration rate in patients with volume depletion or renal artery stenosis, thus limiting the delivery of sodium and water to the distal nephron, which, in combination with hypoaldosteronism may promote hyperkalemia [80]. In patients with normal renal function serum potassium rarely increases by more than 0.5 mmol/L [80,81]. In patients with diminished renal function, the rise in potassium concentration may be more marked, since the increase is usually inversely related to GFR [89], particularly in patients with hyporeninemic hypoaldosteronism (e.g. in diabetic nephropathy), in patients on beta-adrenergic blockers or in patients on potassium-sparing diuretics [82, 89-92]. Furthermore, depletion of the effective plasma volume, such as that observed in heart failure or cirrhosis, is also an important risk factor for the development of hyperkalemia after ACE inhibitors administration [80]. A recent report showed that the majority of the patients who develop hyperkalemia (serum potassium >5.1 mmol/L) while on these drugs had chronic renal
failure (creatinine clearance <80 ml/min) and diabetes mellitus [93]. The combination of an ACE inhibitor with other drugs affecting potassium homeostasis can also precipitate hyperkalemia [81]. Thus, the combination of potassium-sparing diuretics and ACE inhibitors should be avoided and the effects of potassium supplements on serum potassium concentrations must be closely monitored in elderly patients on ACE inhibitors [83,89,93,48]. It has been suggested that spironolactone dosage must be kept low in the setting of heart failure treatment to avoid serious hyperkalemia [81]. Furthermore, the use of ACE inhibitors (or angiotensin receptor blockers) is independently associated with an increased risk of developing hyperkalemia in hemodialysis patients [94]. Thus, serum potassium levels should be closely monitored when these medications are prescribed for these patients. On the other hand, a reduction in the drug’s dose and the initiation of a low-potassium diet may lower the risk for the development of hyperkalemia [95]. However, a large number of patients with decreased renal function require discontinuation of ACE inhibitors due to hyperkalemia and thus are deprived of their renoprotective effects [93].

There are a limited number of cases of ACE inhibitor-induced hyponatremia [96,97]. The postulated underlying mechanisms are not clear-cut. It has been suggested that in some predisposed individuals the increased angiotensin II levels observed in the CNS after ACE inhibitors administration may play a significant role. In fact, since these drugs cannot cross the blood–brain-barrier, the levels of angiotensin II rises within the brain, thereby centrally stimulating both thirst and the hypothalamic release of vasopressin resulting in hyponatremia. The risk of ACE inhibitors-induced hyponatremia is increased by the concomitant use of thiazides [96,97]. In this setting, it should be mentioned that angiotensin converting enzyme inhibitors have been used in the treatment of congestive heart failure associated with hyponatremia [98].
3. ANGIOTENSIN II RECEPTOR ANTAGONISTS

Angiotensin II receptor antagonists can cause hyperkalemia by inducing a state of hypoaldosteronism similar to ACE inhibitors [80]. Studies have shown that in individuals at low risk to develop hyperkalemia the incidence of increased potassium levels (potassium levels ≥ 5.5 mmol/L) is not different between these two classes of drugs [1.5% with losartan vs 1.3% with ACE inhibitors] [99,100]. In one study Bakris et al showed that in patients with decreased renal function the administration of lisinopril resulted in greater increases in serum potassium levels and decreases in serum aldosterone levels compared to valsartan [101].

4. BETA-ADRENERGIC ANTAGONISTS

Non selective beta-adrenergic antagonists may cause hyperkalemia following a potassium load, severe exercise, or in the presence of hypoaldosteronism or renal failure [103-105]. These drugs alter transcellular partitioning of potassium resulting in a decreased potassium uptake by cells and reduce renin secretion, thereby decreasing aldosterone synthesis [81,103]. Central adrenergic inhibitors, e.g. clonidine, or beta-1-selective blockers, e.g. atenolol, interfere less with potassium homeostasis [106-107].

5. HEPARIN

Prolonged heparin administration may cause hyperkalemia via inhibition of adrenal 18-hydroxylase, which is the final enzymatic step of aldosterone formation. Furthermore, heparin can decrease the number and affinity of angiotensin II receptors in the adrenal zona glomerulosa reducing the main stimulus for aldosterone synthesis [108-111]. Additionally, heparin may induce a progressive atrophy of the zona glomerulosa after long-term administration [111]. Finally, excess anticoagulation with heparin may precipitate adrenal hemorrhage leading to adrenal insufficiently [111]. The risk of hyperkalemia is
exacerbated by the simultaneous administration of ACE inhibitors or the presence of long-standing diabetes mellitus [108, 110-114]. The drug can increase serum potassium by 0.2 mmol/L to as much as 1.7 mmol/L among patients treated for 3 or more days [111]. A recently reported interesting condition is selective hypoaldosteronism in critically hypoxic patients, which predisposes to heparin-induced hyperkalemia [115]. Hyperkalemia is also reported with low-molecular-weight heparin (LMWH) preparations [116,117]. Thus, until more information is available, LMWH does not seem to be a reasonable alternative in patients who develop heparin-induced hyperkalemia. A recent report showed that fludrocortisone is a reasonable alternative therapy for patients with hyperkalemia secondary to heparin therapy when the continuing administration of heparin is necessary [118].

6. DIGITALIS

Digitalis can impair Na\(^+\)-K\(^+\)-ATPase pump activity in a dose-dependent fashion. The drug does not usually lead to hyperkalemia when serum digoxin levels are therapeutic. However, toxic doses, e.g. ingested in a suicide attempt, may cause hyperkalemia that can be fatal [119]. Furthermore, hyperkalemia has been observed in patients who exhibit therapeutic or mildly increased digoxin levels if other factors for impaired potassium handling are present. This increase in potassium levels results from both impaired cellular uptake and reduced renal excretion of potassium [119-122].

7. THEOPHYLLINE

Hypokalemia that possibly reflects stress-induced epinephrine release has been reported in cases of acute theophylline intoxication [123]. Hyponatremia has also been found after theophylline administration. The underlying mechanisms include a thiazide-like action of the drug, especially in the presence of elevated serum concentrations, or, the
stimulation of ADH secretion[124]. Interestingly, theophylline administration is followed by increased urinary losses of phosphate [74].

8. OTHER DRUGS

Hyponatremia due to inappropriate antidiuresis appears to be a rare complication associated with amiodarone therapy [125]. Dobutamine has rarely been associated with hypokalemia [126]. In heart failure, for example, a rapid 0.4meq/L fall in the plasma K⁺ concentration following the administration of dobutamine may cause an exacerbation of ventricular arrhythmias [126]. Moreover, the drug dopamine can cause phosphaturia, although hypophosphatemia has not been reported after dopamine administration.
CONCLUDING REMARKS

Cardiovascular drugs may affect acid-base balance and serum electrolyte levels. These effects need to be considered when managing the large numbers of patients with, or at risk of developing, vascular disease.
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