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REVIEW

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Electrolyte's imbalance role in atrial fibrillation: Pharmacological management

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Abstract

The contribution of the perpetuation of atrial fibrillation is caused by electrical remodeling in which calcium, sodium and potassium channels could refer to changes in the ion channel protein expression, development of fibrosis, gene transcription and ion channel redistribution. Calcium and magnesium could influence the risk of atrial fibrillation which is the leading cause of cardiac death, heart failure and ischemic stroke. The elevated serum concentration of calcium had a higher range of in-patient's mortality, increased total cost of hospitalization and increased length of hospital stay as compared to those without hypercalcemia in atrial fibrillation patients. Moreover, chloride channels could affect homeostasis, atrial myocardial metabolism which may participate in the development of atrial fibrillation. Up to a 50% risk of incidence of AF are higher in which left ventricular hypertrophy, sudden cardiovascular death and overall mortality relate to a low serum magnesium level. Additionally, magnesium prevents the occurrence of AF after cardiac surgery, whereas greater levels of serum phosphorus in the large population-based study and the related calcium–phosphorus products were linked with a greater incidence of AF. Numerous clinical studies had shown the high preoperative risk of AF that is linked with lower serum potassium levels. The conventional risk factor of increased risk of new onset of AF events could independently link with high dietary sodium intake which enhances the fibrosis and inflammation in the atrium but the mechanism remains unknown. Many drugs were used to maintain the electrolyte imbalance in AF patients.

Keywords: AF, Electrolytes, Calcium, Chloride, Magnesium, Phosphorus, Potassium, Sodium

Background

The most common cardiac arrhythmia is atrial fibrillation (AF) which increased the risk of stroke, heart failure and cardiovascular death [1]. There are many risk factors for the development of AF including age, heart failure, hypertension, coronary heart disease, white race, left ventricular hypertrophy, chronic kidney disease (CKD), obesity and certain lifestyle factors [2]. The contribution of the perpetuation of AF is caused by electrical remodeling in calcium, sodium and potassium channels which could refer to changes in the ion channel protein expression, development of fibrosis, gene transcription and ion channel redistribution [3].

Calcium and magnesium could influence the risk of atrial fibrillation which is the leading cause of cardiac death, heart failure and ischemic stroke [4]. In the same way, Alonso et al.'s study had reported the relationship of AF and the burden of supraventricular arrhythmias with circulating electrolytes including calcium, sodium, phosphorous, magnesium, potassium and chlorine. The data are scarcer that explain the relationship between the risk of AF with circulating electrolytes such as potassium, chlorine, calcium and sodium, whereas the increased risk of AF has been related to a higher concentration of phosphorous and lower circulating magnesium concentration. Moreover, the authors had observed a lower prevalence of

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AF among persons with elevated levels of circulating potassium, chloride, phosphorous and magnesium [5].

In the general population, approximately 3% of AF occurring is the well-known risk factor of cardiovascular morbidity and mortality. In the renal failure population, non-valvular AF frequently occurs ranging from 19 to 24% rising to 27% in patients with end-stage renal disease. Numerous studies have implicated atrial fibrillation as a contributing factor in CKD as well as cardiovascular events. The prevalence of coronary artery disease (CAD) in patients with AF varies substantially from 17 to 46% [6].

Google Scholar, PubMed and Science direct were used to review the literature. October 20, 2021, was the late date of the research. Many keywords were used for searching the literature such as AF, electrolytes, calcium, chloride, magnesium, phosphorus, potassium and sodium. The language of clinical studies was restricted to English. This review article focuses to report the recent studies which mainly explained the role of electrolytes (calcium, chloride, magnesium, phosphorus, potassium and sodium) imbalance in AF patients as explained in Fig. 1 and their pharmacological management in AF subjects.

Main text

Role of different electrolytes imbalance in AF

There are many electrolytes which are present in the human body; however, this review article only highlights pathophysiological aspects of major electrolytes such as calcium, chloride, magnesium, phosphorus, potassium and sodium in AF as explained in Fig. 2 and also report the drug management of electrolytes imbalance in AF subjects.

Calcium

Calcium is very important in regulating heartbeat and fluid balance within cells, muscle contraction, oocyte activation, building strong bones and teeth, nerve impulse, transmission and blood clotting within cells. Their requirements are increased during the period of growth including in childhood, during pregnancy and breastfeeding [7].

The intracellular calcium overload was involved in the development of electrical remodeling. It was also suggested to be involved in electrical remodeling largely based on indirect evidence using L-type calcium channel antagonists [8, 9]. In the process of electrical remodeling, mitochondrial calcium accumulation has been implicated

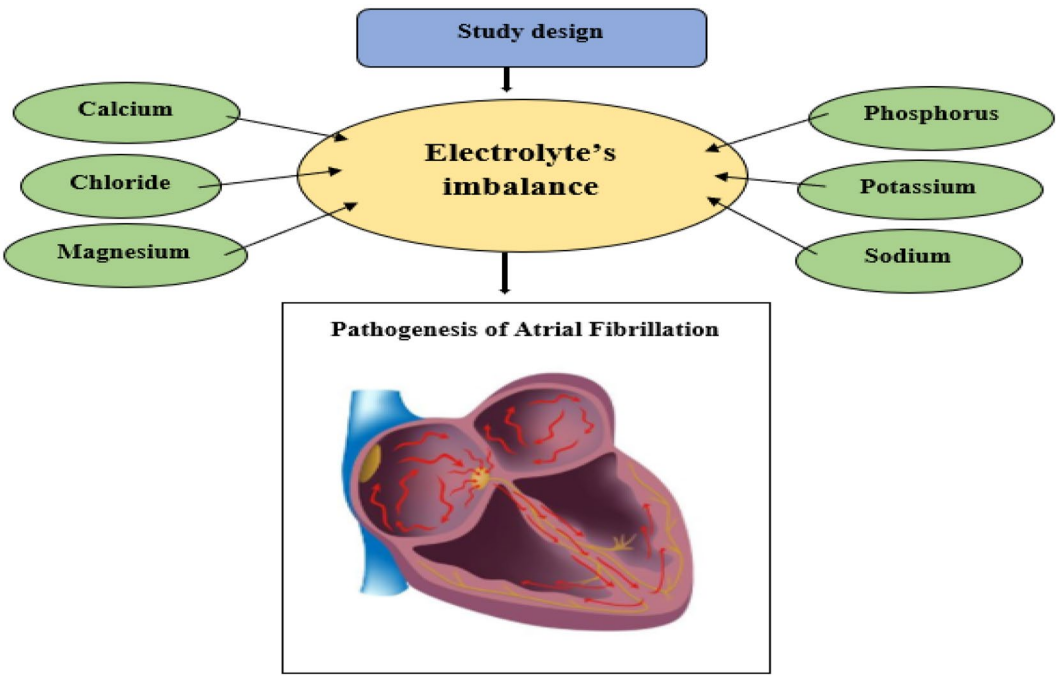

Fig. 1 Overall plan of the review article Source: Designed by the author with the help of review articles

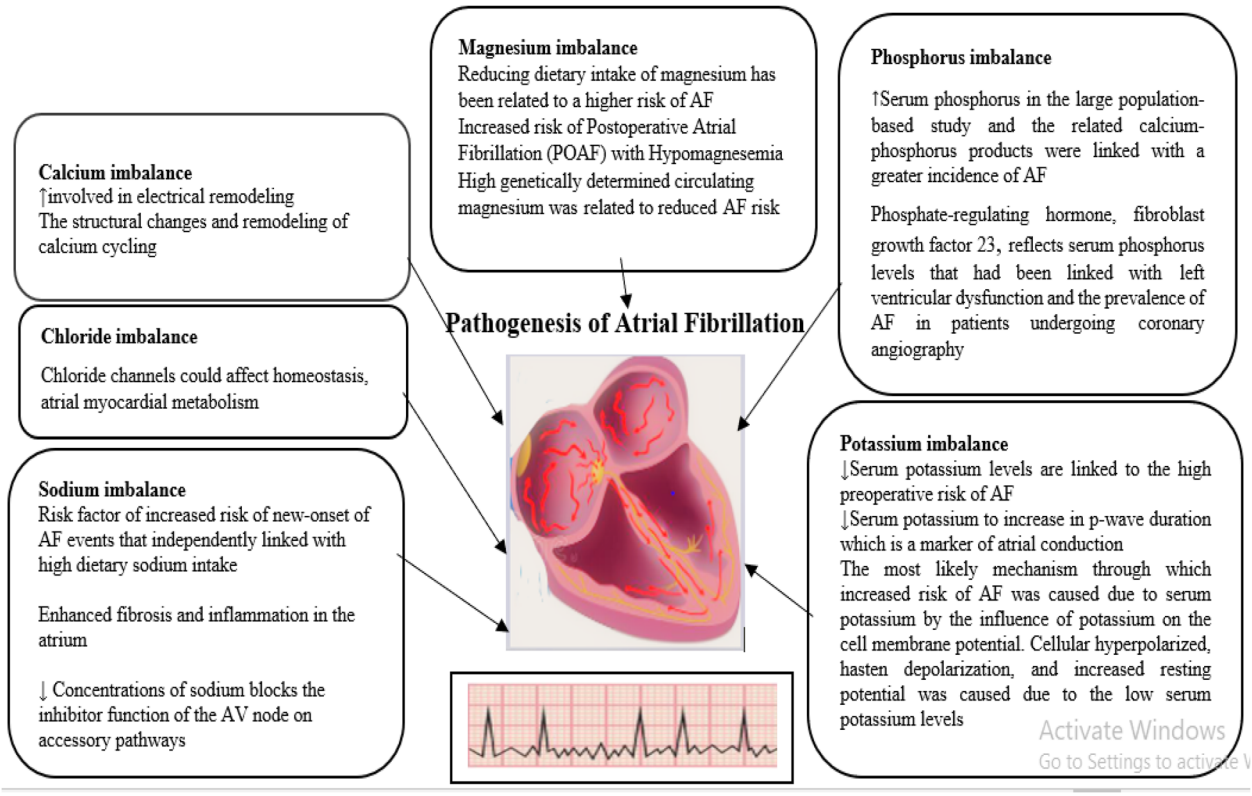

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Fig. 2 Role of major electrolytes imbalance lead pathogenesis of AF Source: Designed by the author with the help of review articles

because mitochondria can buffer large increases in intracellular calcium when cytoplasmic free calcium reaches pathologically high micromolar levels [10].

Small conduction calcium-activated potassium channels are propagated of triggered impulses from the pulmonary veins to the atria that are caused by calcium. The expression of these channels increased due to the rapid stimulation. In the pulmonary veins, an action potential is shortened. Within the atria, heart failure has resulted because of the structural changes and remodeling of calcium cycling which support persistent atrial fibrillation [11]. Hypercalcemia is linked with left ventricular hypertrophy, shortened QT interval, hypertension, vascular calcification and arrhythmias. On the other way, hypocalcemia is related to prolonged QT intervals, heart failure and life-threatening cardiac arrhythmias. Both decreased and increased serum concentrations of calcium are linked with increased mortality [3].

According to the previous studies, AF risk is increased due to a rapid atrial activation rate which induces electrical remodeling. This remodeling consists of upregulation of sodium-calcium exchanger, Ca^{2+} transients are reduced, and reduction of L-type Ca^{2+} current and sarcoplasmic reticulum function altered, characterized by the increased spontaneous Ca^{2+} sparks as well as waves, have been attribution to hyperactive RyR2 channels that possibly as a result of elevated phosphorylation at residues Ser2808 and Ser2815. These increased Ca^{2+} waves as well as leaky RyR2 channels are capable of focal atrial electrical activity and are also triggered delayed after afterdepolarization. Therefore, the most important contributor to the induction and maintenance of AF was the hyperactive RyR2 channels in humans [12].

Deo M et al.'s study had reported in cardiac cells; intracellular calcium dynamics have been recognized as an important contributor in life-threatening ventricular arrhythmia including ventricular fibrillation as well as ventricular tachycardia and increasing the prevalent atrial arrhythmias such as flutter and atrial fibrillation [13].

In the same way, Abed et al.'s study had described the elevated serum concentration of calcium concentration had an elevated range of in-patient's mortality, increased total cost of hospitalization and increased length of hospital stay as compared to those without hypercalcemia in

AF patients. Moreover, the authors have suggested further investigation on the role of calcium serum levels in patients with AF, both as a marker to predict mortality and as a key target of the in-patient therapeutic approach [14].

In AF patients, there are drugs including calcium channel blockers, diltiazem such as Cardizem and verapamil including Calan and Isoptin for the effective for initial ventricular rate control. They have given intravenously in bolus doses until the ventricular rate becomes slower [15]. Also, Heywood et al.'s study stated that calcium channel blockers could have a role in the acute reduction of ventricular response in AF patients that had complications due to heart failure; however, their safety in chronic heart rate control remains to be proven [16].

Moreover, Chao et al. revealed in the nationwide AF cohort, those patients receiving rate control treatment with calcium channel blockers or β-blockers had reduced risk of mortality, whereas it was also associated with the largest risk reduction with the use of β-blockers and greater mortality was linked with the use of digoxin. However, to confirm these findings, randomized and prospective trials are required [17].

At the cell membrane, verapamil acts to inhibit transmural fluxes of calcium that slow ventricular response in AF by inhibiting the atrioventricular conduction. When serum calcium level rises to abnormal levels, this effect is abolished in AF patients and slowing of the ventricular response is achieved by reducing serum calcium, whereas verapamil treatment was maintained [18].

Chloride

After sodium, the most abundant electrolytes in serum is the chlorine which has a key role in the regulation of body fluids, acid-base status, electrolyte balance, and the preservation of electrical neutrality. Also, it is an essential component for the assessment of various pathological conditions. Abnormal chloride levels play role in more serious underlying metabolic disorders including alkalosis or acidosis [19].

Atrial fibrillation begins from paroxysmal to progressing form through persistent to permanent type with structural and electrical atrial remodeling [20, 21]. The maladaptive process is the left atrial remodeling which includes collagen accumulation, apoptosis, fibroblast proliferation and myocytes hypertrophy [22]. In addition, various studies had focused on the processes responsible for atrial fibrillation changes in the ion channels in the cell membrane and also in the electrophysiological properties of atrial tissues. It has been reported that in the atrial myocytes changes in the channels mainly include Ca^{2+}, K^{+} and Na^{+} ion channels [23].

Moreover, the function of chlorine channels involves cell volume regulation, regulation of excitability, ionic homeostasis, transepithelial transport, etc., in the plasma membrane [24]. Duan et al. reported that the chloride channel was related to various cardiovascular diseases including hypertension, ischemic, myocardial hypertrophy and heart failure [25].

The evidence of the significance of chloride intracellular channel 4 (CLIC4) was involved in cellular differentiation, endothelial tubulogenesis, apoptosis and inflammation. CLIC4 expresses in cardiomyocytes, lung alveolar septae and vascular endothelial cells [26]. By modulating mitochondrial function, chloride channels play an important role in cardioprotection from ischemic-reperfusion injury and cardiac function. Additionally, Jiang et al.'s study demonstrated the upregulated CLIC1,4,5 is differentially expressed in patients with atrial fibrillation. The authors indicate in results that chloride channels could affect homeostasis, atrial myocardial metabolism and also participate in the development of atrial fibrillation [27].

In the same way, Kolkebeck et al.'s study was determined whether calcium chloride (CaCl (2)) pretreatment would blunt an SBP drop after i.v. diltiazem, while allowing diltiazem to maintain its efficacy. A prospective, randomized, double-blind, placebo-controlled study was conducted. Although i.v. CaCl (2) seems to be equally safe compared to placebo as a pretreatment in the management of atrial fibrillation or flutter (AFF) with the rapid ventricular response (RVR), the authors were unable to find a statistically significant blunting of SBP drop with CaCl (2) i.v. pretreatment. Until further research determines, a benefit exists. Moreover, authors cannot recommend i.v. CaCl (2) pretreatment before diltiazem in the treatment of AFF with rapid ventricular response [28].

Also, Jiang et al.'s study had indicated that chloride intracellular channels (CLICs) play an important role in the development of atrial fibrillation. Chloride intracellular channels and structural type IV collagen may interact with each other to promote the development of AF in rheumatic mitral valve disease [27]. Hansen et al.'s study had explained the quantitative PCR experiments using human heart tissue from healthy donors demonstrated that *CLCN2* is expressed across all four heart chambers. Authors explain the genetic and functional data points to a possible link between loss of ClC-2 function and an increased risk of developing AF [29]. The novel finding

is that intracellular chlorine accumulation is induced by rapid pacing and may play a role in AF pathogenesis by causing resting membrane depolarization and effective refractory period (ERP) reduction [30].

Magnesium

The fourth most important and abundant cation is the magnesium in the human body as well as intracellular tissues and also the second most prevalent cation. Many physiologic roles of magnesium involve in protein transport, enzyme activity and become an essential part of all adenosine triphosphate-utilization systems. It is related to cardiovascular disorders; for example, reducing dietary intake of magnesium has been related to a higher risk of AF, hypertension, ischemic heart disease, heart failure-related hospitalization and new-onset heart failure. On the different organ systems, magnesium has various significant pharmacological as well as physiological effects that involve the mechanism of action such as membrane stabilization, calcium antagonism and regulation of energy transfer [31].

Moreover, up to a 50% risk of incidence of AF are higher, in which left ventricular hypertrophy, sudden cardiovascular death and overall mortality relate to a low serum magnesium level. Intravenous magnesium directly affects myocardial potassium channels, prolongs the PR interval, has voltage-dependent and indirect effects on sodium and calcium channels and elevated the refractory period of antegrade atrioventricular node conduction [32, 33].

Misialek et al. reported that the increased risk of cardiovascular disease (CVD) is linked with low serum magnesium that includes ventricular arrhythmias. In conclusion, the authors showed that a higher risk of atrial fibrillation was related to low serum Mg, not with dietary Mg [34].

Additionally, Crippa and Rasmussen's studies had reported that intravenous magnesium has a high therapeutic to toxic ratio and minimal negative inotropic effects [35, 36]. It is also reduced the automaticity [37], atrioventricular nodal conduction, digoxin-induced arrhythmias and prolonged QT interval which are caused by polymorphic ventricular tachycardia. The occurrence of AF after cardiac surgery could also be reduced due to the prophylactic use of intravenous magnesium. Intravenous magnesium as compared to other antiarrhythmic agents or with digoxin is not effective in converting acute onset AF to sinus rhythm in subjects with a normal serum magnesium concentration [38]. Also, Miller et al.'s study has been demonstrated a meta-analysis that shows magnesium in preventing the occurrence of AF after cardiac surgery [39].

Various studies had reported a significant association between a higher risk of postoperative atrial fibrillation (POAF) and low preoperative intracellular magnesium concentrations [40, 41]. The 16 percent was a range of incidence of postoperative atrial fibrillation. The multivariate risk of postoperative AF was increased fivefold due to the rate of myocardial extraction of intracellular magnesium which was $\geq 7\%$ that might be a new and potent predictive factor for postoperative AF [40].

In the same way, Henyan et al. had suggested that the risk of POAF was reduced due to the lower doses of magnesium (OR 0.36, 95% CI 0.23–0.56). On the other hand, moderate-high doses did not reduce the risk of postoperative AF (OR 0.99, 95% CI 0.70–1.42), whereas no trials have directly compared the impact of either various magnesium dosing strategies or timing on postoperative atrial fibrillation risk and it gave a significant knowledge gap [42].

The development of AF in individuals without CVDs is linked to the lower serum magnesium because hypomagnesemia is common and is associated with AF which could have potential clinical implications [43]. Moreover, a meta-analysis had revealed that the incidence of postoperative AF was about 36 percent due to the reduced intravenous magnesium [44].

Furthermore, Tercius et al.'s study had demonstrated that concurrent use of magnesium enhances the ability of ibutilide to successfully convert AF or flutter. The greatest benefit had appeared due to the 4 g of magnesium dose. Previous studies had been reported the relationship of increased risk of postoperative atrial fibrillation (POAF) with hypomagnesemia [45]. In contrast, Klinger et al.'s study had concluded that the incidence of new-onset POAF after cardiac surgery does not decrease due to the high-dose intraoperative Mg therapy [46]. Moreover, Rajagopalan et al.'s study had concluded that Mg infusion does not increase the rate of successful cardioversion in patients undergoing electric cardioversion for persistent AF [47].

In the same way, Arsenault et al.'s study had reported the reduced risk of postoperative AF with oral magnesium supplementation [48], whereas Larsson et al.'s study revealed in Mendelian randomization analysis to show high genetically determined circulating magnesium which was related to reducing the atrial fibrillation risk [49].

For years in clinical medicines, to stop or treat arrhythmias, magnesium supplements play their role by preventing atrial fibrillation following cardiac surgery, refractory ventricular fibrillation, acute treatment of rapid AF, new-onset and treatment-refractory supraventricular tachycardia (SVT), and a variety of drug-induced arrhythmias including torsade de points

(TdP); magnesium has been incorporating into their recent guidelines for managing as well as preventing certain arrhythmias [50].

Furthermore, Ho et al.'s study had reported in a meta-analysis showing that adding intravenous magnesium to either ibutilide or digoxin was not effective in achieving sinus rhythm once atrial fibrillation has developed. As a result, the therapeutic effect of intravenous magnesium is mainly on reducing the fast ventricular response rate in subjects with acute AF [38].

Phosphorus

Phosphorus is an essential mineral that is naturally present in many foods and available as a dietary supplement. Phosphorus is a component of bones, teeth, DNA, and RNA [51]. It is important for many biologic functions, such as energy exchange, cellular signal transduction as well as mineral metabolism and also is an independent predictor of atrial fibrillation [52].

Various studies have been reported that elevated phosphorous levels were associated with coronary arteries, increased left ventricular mass, carotid atherosclerosis, increased arterial stiffness and calcification of the aorta [53–59]. It also increased cardiovascular mortality and morbidity in patients with and without chronic kidney diseases [55, 57, 60, 61]. Lopez et al.'s study had concluded the greater levels of serum phosphorus in the large population-based study and the related calcium–phosphorus products were linked with a greater incidence of AF [62].

Numerous potential processes could explain the greater phosphorus levels with increased risk of AF. Firstly, coronary arteries and calcification of the aorta had been associated with the excess phosphorus levels [58, 59], thereby directly promoting vascular injury, smooth muscle proliferation and elevated vascular calcification which can lead to a greater risk of AF. Secondly, the inhibition of 1,25-dihydroxy vitamin D synthesis is caused due to the high levels of phosphorus [63] and it has been hypothesized that decreased cardiac contractility, as well as increased coronary calcification, could cause the lower levels of 1,25-dihydroxy vitamin D [64, 65], which might lead to the increased the risk of AF. Thirdly, secondary hyperparathyroidism has been linked to excess phosphorus which might involve increased circulating levels of parathyroid hormone which in return could increase the proinflammatory processes that lead to an increased risk of AF. Similarly, a recent cross-sectional study also demonstrated that parathyroid hormone levels were elevated in patients with atrial fibrillation as compared to controls in sinus rhythm [66].

Various mechanisms could mediate the relationship between AF and serum phosphorus levels, such as the greater risk of heart failure and increased left ventricular mass in those with elevated phosphorus concentrations [55]. Finally, a phosphate-regulating hormone, fibroblast growth factor 23, reflects serum phosphorus levels that had been linked with left ventricular dysfunction and the prevalence of AF in patients undergoing coronary angiography [67].

Potassium

Potassium (K) is an important macromineral nutrient and principal cation in intracellular fluid, which regulates the osmotic pressure; muscle contraction participates in acid–base balance, cell membrane function and more in human. A high dietary intake of potassium has a protective role against the kidneys, cardiovascular system and bones diseases [68].

The risk of cardiovascular disease has increased especially cardiac arrest and ventricular arrhythmias that had shown an association with serum potassium (< 3.5 mmol/l), especially in hypokalemia [69]. Various studies had reported the relationship between the risk of AF and serum potassium. Moreover, numerous clinical studies had shown that the high preoperative risk of AF was linked with lower serum potassium levels [70, 71]. However, other populations studies did not show an association between them [72, 73]. Additionally, Severi et al.'s study found decreased serum potassium to increase in p-wave duration which is a marker of atrial conduction in hemodialysis patients [74].

Moreover, Krijthe et al.'s study also reported a link between increased risk of AF with hypokalemia (< 3.50 mmol/l) in comparison with ormokalemia [75]. Moreover, Auer et al.'s study had revealed a relationship of lower serum potassium (< 3.9 mmol/l) with increased risk of AF during the postoperative period [71]. Numerous studies had been investigated the influence of potassium in the progress of AF. Wahr et al.'s study explained among 2402 patients undergoing cardiac surgery reports the association of AF with preoperative hypokalemia (< 3.5 mmol/l) as compared to elevated levels of AF [70]. Also, Madias et al.'s study stated the higher risk of AF was not linked with hypokalemia during hospitalization as compared to normokalemia and included 517 patients with acute myocardial infarction. The most likely mechanism through which increased risk of AF was caused due to serum potassium, which includes the influence of potassium on the cell membrane potential, cellular hyperpolarized, hasten depolarization and increased resting potential triggered due to the low serum potassium levels [72, 76].

In the same way, Worthley et al.'s study stated the resting membrane potential is happened due to the extracellular potassium concentration; therefore, it has a large impact on myocardial tissue excitability. Intravenous

potassium is often used to treat hypokalaemia cardiac arrhythmias as the cardiac effects of hypokalaemia include excitability and contractility changes [77].

The anatomical or functional obstacle is caused due to initiation of re-entry, rise ectopic beats that resulted in the abnormal excitability in myocardial cells. The repolarization process of the cardiac action potential (AP) is controlled by potassium currents, membrane potential, refractoriness of the myocardium which is also determined by potassium channel functions. Both loss and gain of the potassium channel function could lead to arrhythmia. These are three pathophysiological relevant aspects that pro-arrhythmic consequences of malfunction potassium channels in atria and ventricular tissue. It has been resulted due to drug action, disease-induced remodeling and genetic background. The increased risk of sudden cardiac death is due to heart failure and the downregulation of potassium channels. Polymorphism and mutations in genes encoding for atrial potassium channels could be linked with loss of function, gain of function and shortened and prolonged action potential duration. The particular therapeutic challenge has become due to the block of atrial potassium channels when trying to better atrial fibrillation. This arrhythmia has a strong tendency to cause electrical remodeling that affects various potassium channels [78].

Additionally, Tazmini et al.'s study had reported that increasing plasma-potassium levels did not significantly enhance the conversion of recent-onset atrial fibrillation (ROAF) or atrial flutter to sinus rhythm in subjects with potassium levels in the lower-normal range; authors revealed in results that treatment could be effective when a rapid increase in potassium levels is achieved and tolerated [79].

Sodium

Sodium allows to build up an electrostatic charge on cell membranes as well as transmission of nerve impulse when the charge is allowed to dissipate by a moving wave of voltage change in the organism. It is also classified as a dietary inorganic micromineral for animals [80]. Moreover, Frisoli et al.'s study had stated the independent relation of blood pressure and high salt intake that could increase the risk of heart failure, stroke, proteinuric renal disease and left ventricular hypertrophy (LVH) [81].

The conventional risk factor of increased risk of new onset of atrial fibrillation events is independently linked with high dietary sodium intake. They had reported the first study about the relationship between the cumulative incidence of AF events and dietary sodium intake. It is also possible that AF is connected with sodium intake which enhances fibrosis and inflammation in the atrium but the mechanism remains unknown [82]. Similarly, Cavusoglu et al.'s study reported that hyponatremia was independently related to the occurrence of atrial fibrillation [83].

The occurrence of AF had increased the hypokalemia and hyponatremia. Pulmonary veins and sinoatrial nodes play a critical role in the pathophysiology of AF. So, low sodium, as well as low potassium, was differentially modulated pulmonary veins and sinoatrial node electrical properties. Low sodium and low potassium-induced slowing of sinoatrial node beating rate and genesis of pulmonary veins burst firing which could contribute to the higher occurrence of AF during hyponatremia or hypokalemia [84]. In addition, Takase et al.'s study also highlights the association of salt intake with the presence and development of AF in the general population, including other factors rather than salt intake had a much more prominent impact on the progress of AF. Further, the authors had been suggested the complementary role of salt intake for the prediction of atrial fibrillation [85].

There are certain clinical entities, including chronic heart failure, pneumonia, coronary artery bypass surgery, chronic kidney disease and hypomagnesemia, all of which could result in hyponatremia which also predispose the patient to the process of atrial fibrillation. There was a strong negative correlation between serum sodium level and heart rate. The main cause of hyponatremia was the reason for the high ventricular rate in patients with lower concentrations of sodium that blocks the inhibitor function of the AV node on accessory pathways [86].

Various clinical cardiac disorders are linked with the rise of the intracellular Na concentration (Na_i) in heart muscle. A clear example is the digitalis toxicity in which excessive inhibition of the NA/K pump causes the raised of sodium concentration as compared to a normal level. Moreover, the rise of sodium concentration could be an important contributor that caused to increase the cardiac arrhythmias [87].

Oulu project Elucidating Risk of Atherosclerosis (OPERA) cohort study had been evaluated the relationship between the incidence of new-onset AF and dietary sodium intake during a mean follow-up of 19 years among 716 subjects. The main finding indicates that the long-term risk of new-onset AF was linked to sodium intake but further confirmatory studies are required [82].

Moreover, Dudenbostel et al. demonstrated a significant relationship between AF in PA patients with a lower 24-h urinary sodium-to-potassium ratio (24hUNak). There were benefits for an increase in potassium, and reduction in sodium has been shown in patients with hypertension. Using the UNak ratio as a tool that improves through medical therapy and diet including mineralocorticoid receptor antagonism could be key to stopping atrial fibrillation [88].

Serious complications have been reported due to the AF including thromboembolism, congestive heart failure and myocardial infarction. To prevent the adverse consequences of AF, it is important to recognize and acute management of AF in the physician's office or emergency department [89]. There is the majority of antiarrhythmic drugs available that exert predominant effects on cardiac potassium or sodium currents. The membrane-stabilizing agents are sodium channel blocking drugs because the excitability of cardiac tissue is decreased by them. Quinidine, as well as disopyramide, affects conduction including sodium channel blockade in case of rapid heart rates. Also, these drugs have intermediate sodium channel blocking activity and exhibit use dependence. These agents largely affect potassium channels (I_{kr}) at normal or slow heart rates, low concentrations and also display reverse use dependence for potassium [90].

A century ago, Quinidine was used as a potential antiarrhythmic drug. It is a vagolytic and blocking agent with an intermediate sodium channel blocking effect at rapid heart rates, higher concentration, at slower heart rates, has potassium channel blocking effect and normal concentration and is rarely used for AF. Disopyramide drugs blocking the sodium channel and prescriptions represent 1% to 2% of annual antiarrhythmic drug prescriptions in the USA [91]. Without structural heart disease, flecainide and propafenone are recommended for the management of patients with atrial fibrillation [92].

At present, it is represented 10% of annual US antiarrhythmic drug prescriptions. Flecainide has a significant activity for sodium channel blocking and has mild I_{kr} blocking effects but is not related to significant QT prolongation. It has mild negative inotropic effects and like propafenone, and it is linked with a significant incidence of atrial flutter [90, 93, 94].

Conclusion

This review concludes that electrolytes imbalance plays a significant role in the pathogenesis of atrial fibrillation. To manage the electrolytes imbalance in AF subjects, numerous drugs were used. Future studies need to find the exact mechanism of these electrolytes in AF. More research studies are required to find the diet management of these electrolytes in AF subjects.

Abbreviations

AF: Atrial fibrillation; CLIC4: Chloride intracellular channel 4; CVD: Cardiovascular disease; POAF: Postoperative atrial fibrillation; LVH: Left ventricular hypertrophy; SVT: Supraventricular tachycardia.

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Author contributions

SRM carried out the study design and data collection. SR and HK wrote the manuscript. All authors read and approved the final manuscript. SR gave the editing services of the manuscript.

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Competing interests

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References

1. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA. 1994;271(11):840–4.
2. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004;292(20):2471–7.
3. Lee HC. Electrical remodeling in human atrial fibrillation. Chin Med J. 2013;126(12):2380–3.
4. Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of magnesium in cardiovascular diseases. Cardiol Rev. 2014;22(4):182–92.
5. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158(1):111–7.
6. Tomaszuk-Kazberuk A, Nikas D, Lopatowska P, Młodawska E, Malyszko J, Bachorzewska-Gajewska H, Dobrzycki S, Sobkowicz B, Goudevenos I. Patients with atrial fibrillation and chronic kidney disease more often undergo angioplasty of left main coronary artery–a 867 patient study. Kidney Blood Press Res. 2018;43(6):1796–805.
7. Pravina P, Sayaji D, Avinash M. Calcium and its role in human body. Int J Res Pharmaceut Biomed Sci. 2013;4(2):659–68.
8. Goette A, Honeycutt C, Langberg JJ. Electrical remodeling in atrial fibrillation: time course and mechanisms. Circulation. 1996;94(11):2968–74.
9. Tieleman RG, De Langen CD, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ, Wijffels MC, Allessie MA, Crijns HJ. Verapamil reduces tachycardia-induced electrical remodeling of the atria. Circulation. 1997;95(7):1945–53.
10. Horikawa Y, Goel A, Somlyo AP, Somlyo AV. Mitochondrial calcium in relaxed and tetanized myocardium. Biophys J. 1998;74(3):1579–90.
11. Denham NC, Pearman CM, Caldwell JL, Madders GW, Eisner DA, Trafford AW, Dibb KM. Calcium in the pathophysiology of atrial fibrillation and heart failure. Front Physiol. 2018;9:1380.

12. Gomez-Hurtado N, Knollmann BC. Calcium in atrial fibrillation—pulling the trigger or not? J Clin Investig. 2014;124(11):4684–6.
13. Deo M, Weinberg SH, Boyle PM. Calcium dynamics and cardiac arrhythmia. Clin Med Insight: Cardiol. 2017. https://doi.org/10.1177/1179546817739523.
14. Abed R, Nassar R, Lam PW. Hypercalcemia is a predictor of worse in-hospital outcomes in patients with atrial fibrillation a 2016 national inpatient sample analysis. J Am Coll Cardiol. 2020;75(11_Supplement_1):337–337.
15. Prystowsky EN, Benson DW Jr, Fuster V, Hart RG, Kay GN, Myerburg RJ, Naccarelli GV, Wyse DG. Management of patients with atrial fibrillation: a statement for healthcare professionals from the Subcommittee on Electrocardiography and Electrophysiology. Am Heart Associat Circulat. 1996;93(6):1262–77.
16. Heywood JT. Calcium channel blockers for heart rate control in atrial fibrillation complicated by congestive heart failure. Can J Cardiol. 1995;11(9):823–6.
17. Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE. Rate-control treatment and mortality in atrial fibrillation. Circulation. 2015;132(17):1604–12.
18. Cheungpasitporn W, Jirajariyavej T, Chanprasert S. Rate control medications for atrial fibrillation in the setting of hypercalcemia. Am J Emerg Med. 2011;29(7):830.
19. Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? Eur J Intern Med. 2012;23(3):203–11. https://doi.org/10.1016/j.ejim.2011.11.013 (**Epub 2011 Dec 21 PMID: 22385875**).
20. Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, Boone J, Sheldon R, Dorian P, Newman D. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. Am Heart J. 2005;149(3):489–96.
21. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, Packer DL, Hammill SC, Shen WK, Gersh BJ. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. Circulation. 2007;115(24):3050–6.
22. Lee YL, Blaha MJ, Jones SR. Statin therapy in the prevention and treatment of atrial fibrillation. J Clin Lipidol. 2011;5(1):18–29.
23. Rozmaritsa N, Christ T, Van Wagoner DR, Haase H, Stasch JP, Matschke K, Ravens U. Attenuated response of L-type calcium current to nitric oxide in atrial fibrillation. Cardiovasc Res. 2014;101(3):533–42.
24. Jentsch TJ, Stein V, Weinreich F, Zdebik AA. Molecular structure and physiological function of chloride channels. Physiol Rev. 2002;82:503–68.
25. Duan DD. The ClC-3 chloride channels in cardiovascular disease. Acta Pharmacol Sin. 2011;32(6):675–84.
26. Padmakumar VC, Masiuk KE, Luger D, Lee C, Coppola V, Tessarollo L, Hoover SB, Karavanova I, Buonanno A, Simpson RM, Yuspa SH. Detection of differential fetal and adult expression of chloride intracellular channel 4 (CLIC4) protein by analysis of a green fluorescent protein knock-in mouse line. BMC Dev Biol. 2014;14(1):1–17.
27. Jiang YY, Hou HT, Yang Q, Liu XC, He GW. Chloride channels are involved in the development of atrial fibrillation–A transcriptomic and proteomic study. Sci Rep. 2017;7(1):1–12.
28. Kolkebeck T, Abbrescia K, Pfaff J, Glynn T, Ward JA. Calcium chloride before iv diltiazem in the management of atrial fibrillation. J Emerg Med. 2004. https://doi.org/10.1016/j.jemermed.2003.12.020.
29. Hansen TH, Yan Y, Ahlberg G, Vad OB, Refsgaard L, Dos Santos JL, Mutsaers N, Svendsen JH, Olesen MS, Bentzen BH, Schmitt N. A novel loss-of-function variant in the chloride ion channel gene Clcn2 associates with atrial fibrillation. Sci Rep. 2020;10(1):1.
30. Akar JG, Everett TH, Ho R, Craft J, Haines DE, Somlyo AP, Somlyo AV. Intracellular chloride accumulation and subcellular elemental distribution during atrial fibrillation. Circulation. 2003;107(13):1810–5.
31. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. Br J Anaesth. 1999;83(2):302–20.
32. Bara M, Guiet-Bara A, Durlach J. Regulation of sodium and potassium pathways by magnesium in cell membranes. Magnes Res. 1993;6(2):167–77.
33. Kulick DL, Hong R, Ryzen E, Rude RK, Rubin JN, Elkayam U, Rahimtoola SH, Bhandari AK. Electrophysiologic effects of intravenous magnesium in patients with normal conduction systems and no clinical evidence of significant cardiac disease. Am Heart J. 1988;115(2):367–73.
34. Misialek JR, Lopez FL, Lutsey PL, Huxley RR, Peacock JM, Chen LY, Soliman EZ, Agarwal SK, Alonso A. Serum and dietary magnesium and incidence of atrial fibrillation in whites and in African Americans-atherosclerosis risk in communities (ARIC) study–. Circulat J. 2012. https://doi.org/10.1161/circ.125.suppl_10.AP111.
35. Crippa G, Sverzellati E, Giorgi-Pierfranceschi M, Carrara GC. Magnesium and cardiovascular drugs: interactions and therapeutic role. Annali italiani di medicina interna: organo ufficiale della SocietÃ italiana di medicina interna. 1999;14(1):40–5.
36. Rasmussen HS, Larsen OG, Meier K, Larsen J. Hemodynamic effects of intravenously administered magnesium on patients with ischemic heart disease. Clin Cardiol. 1988;11(12):824–8.
37. Iseri LT, Allen BJ, Ginkel ML, Brodsky MA. Ionic biology and ionic medicine in cardiac arrhythmias with particular reference to magnesium. Am Heart J. 1992;123(5):1404–9.
38. Ho KM, Sheridan DJ, Paterson T. Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. Heart. 2007;93(11):1433–40.
39. Miller S, Crystal E, Garfinkle M, Lau C, Lashevsky I, Connolly SJ. Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. Heart. 2005;91(5):618–23.
40. Abdel-Massih TE, Sarkis A, Sleilaty G, El Rassi I, Chamandi C, Karam N, Haddad F, Yazigi A, Madi-Jebara S, Yazbeck P, El Asmar B. Myocardial extraction of intracellular magnesium and atrial fibrillation after coronary surgery. Int J Cardiol. 2012;160(2):114–8.
41. Reinhart RA, Marx JJ Jr, Broste SK, Haas RG. Myocardial magnesium: relation to laboratory and clinical variables in patients undergoing cardiac surgery. J Am Coll Cardiol. 1991;17(3):651–6.
42. Henyan NN, Gillespie EL, White CM, Kluger J, Coleman CI. Impact of intravenous magnesium on post-cardiothoracic surgery atrial fibrillation and length of hospital stay: a meta-analysis. Ann Thorac Surg. 2005;80(6):2402–6.
43. Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, Magnani JW, Ellinor PT, Benjamin EJ, Wang TJ. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. Circulation. 2013;127(1):33–8.
44. Gu WJ, Wu ZJ, Wang PF, Aung LHH, Yin RX. Intravenous magnesium prevents atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 7 double-blind, placebo-controlled, randomized clinical trials. Trials. 2012;13(1):1–8.
45. Tercius AJ, Kluger J, Coleman CI, Michael White C. Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. Pacing Clin Electrophysiol. 2007;30(11):1331–5.
46. Klinger RY, Thunberg CA, White WD, Fontes M, Waldron NH, Piccini JP, Hughes GC, Podgoreanu MV, Stafford-Smith M, Newman MF, Mathew JP. Intraoperative magnesium administration does not reduce postoperative atrial fibrillation after cardiac surgery. Anesth Analg. 2015;121(4):861.
47. Rajagopalan B, Shah Z, Narasimha D, Bhatia A, Kim CH, Switzer DF, Gudleski GH, Curtis AB. Efficacy of intravenous magnesium in facilitating cardioversion of atrial fibrillation. Circulat: Arrhyth Electrophysiol. 2016;9(9):003968.
48. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2013. https://doi.org/10.1002/14651858.CD003611.pub3.
49. Larsson SC, Drca N, Michaëlsson K. Serum magnesium and calcium levels and risk of atrial fibrillation: a mendelian randomization study. Circulat Genom Precis Med. 2019;12(1):e002349.
50. Baker WL. Treating arrhythmias with adjunctive magnesium: identifying future research directions. Eur Heart J-Cardiovas Pharmacothe. 2017;3(2):108–17.
51. Erdman JW Jr, Macdonald IA, Zeisel SH, editors. Present knowledge in nutrition. New Jersey: Wiley; 2012.
52. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation. 2005;112(17):2627–33.
53. Onufrak SJ, Bellasi A, Shaw LJ, Herzog CA, Cardarelli F, Wilson PW, Vaccarino V, Raggi P. Phosphorus levels are associated with subclinical atherosclerosis in the general population. Atherosclerosis. 2008;199(2):424–31.
54. Saab G, Whooley MA, Schiller NB, Ix JH. Association of serum phosphorus with left ventricular mass in men and women with stable cardiovascular disease: data from the Heart and Soul Study. Am J Kidney Dis. 2010;56(3):496–505.

55. Dhingra R, Gona P, Benjamin EJ, Wang TJ, Aragam J, D'Agostino RB Sr, Kannel WB, Vasan RS. Relations of serum phosphorus levels to echocardiographic left ventricular mass and incidence of heart failure in the community. Eur J Heart Fail. 2010;12(8):812–8.
56. Ix JH, De Boer IH, Peralta CA, Adeney KL, Duprez DA, Jenny NS, Siscovick DS, Kestenbaum BR. Serum phosphorus concentrations and arterial stiffness among individuals with normal kidney function to moderate kidney disease in MESA. Clin J Am Soc Nephrol. 2009;4(3):609–15.
57. Foley RN, Collins AJ, Herzog CA, Ishani A, Kalra PA. Serum phosphorus levels associate with coronary atherosclerosis in young adults. J Am Soc Nephrol. 2009;20(2):397–404.
58. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–83.
59. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol. 2002;39(4):695–701.
60. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607–17.
61. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO4, Ca× PO4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001;12(10):2131–8.
62. Lopez FL, Agarwal SK, Grams ME, Loehr LR, Soliman EZ, Lutsey PL, Chen LY, Huxley RR, Alonso A. Relation of serum phosphorus levels to the incidence of atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] study). Am J Cardiol. 2013;111(6):857–62.
63. Portale AA, Halloran BP, Morris RC. Physiologic regulation of the serum concentration of 1, 25-dihydroxyvitamin D by phosphorus in normal men. J Clin Investig. 1989;83(5):1494–9.
64. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Körfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol. 2003;41(1):105–12.
65. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation. 1997;96(6):1755–60.
66. Rienstra M, Lubitz SA, Zhang ML, Cooper RR, Ellinor PT. Elevation of parathyroid hormone levels in atrial fibrillation. J Am Coll Cardiol. 2011;57(25):2542–3.
67. Seiler S, Cremers B, Rebling NM, Hornof F, Jeken J, Kersting S, Steimle C, Ege P, Fehrenz M, Rogacev KS, Scheller B. The phosphatonin fibroblast growth factor 23 links calcium–phosphate metabolism with left-ventricular dysfunction and atrial fibrillation. Eur Heart J. 2011;32(21):2688–96.
68. Chang A, Appel LJ. Effects of sodium and potassium intake on health outcomes. Nat Rev Nephrol. 2013;9(7):376–7.
69. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? J Am Coll Cardiol. 2004;43(2):155–61.
70. Wahr JA, Parks R, Boisvert D, Comunale M, Fabian J, Ramsay J, Mangano DT. Multicenter study of perioperative ischemia research group, multicenter study of perioperative ischemia research group preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. JAMA. 1999;281(23):2203–310.
71. Auer J, Weber T, Berent R, Lamm G, Eber B. Serum potassium level and risk of postoperative atrial fibrillation in patients undergoing cardiac surgery. J Am Coll Cardiol. 2004;44(4):938–9.
72. Madias JE, Shah B, Chintalapally G, Chalavarya G, Madias NE. Admission serum potassium in patients with acute myocardial infarction: its correlates and value as a determinant of in-hospital outcome. Chest. 2000;118(4):904–13.
73. Nordrehaug JE, Von Der Lippe G. Serum potassium concentrations are inversely related to ventricular, but not to atrial, arrhythmias in acute myocardial infarction. Eur Heart J. 1986;7(3):204–9.
74. Severi S, Pogliani D, Fantini G, Fabbrini P, Vigano MR, Galbiati E, Bonforte G, Vincenti A, Stella A, Genovesi S. Alterations of atrial electrophysiology induced by electrolyte variations: combined computational and P-wave analysis. Europace. 2010;12(6):842–9.
75. Krijthe BP, Heeringa J, Kors JA, Hofman A, Franco OH, Witteman JC, Stricker BH. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam study. Int J Cardiol. 2013;168(6):5411–5.
76. Schulman M, Narins RG. Hypokalemia and cardiovascular disease. Am J Cardiol. 1990;65(10):E4–9.
77. Worthley LI, Redman J. Antiarrhythmic and haemodynamic effects of the commonly used intravenous electrolytes. Crit Care Resuscit. 2001;3(1):22–34.
78. Ravens U, Cerbai E. Role of potassium currents in cardiac arrhythmias. Europace. 2008;10(10):1133–7.
79. Tazmini K, Fraz MSA, Nymo SH, Stokke MK, Louch WE, Øie E. Potassium infusion increases the likelihood of conversion of recent-onset atrial fibrillation—A single-blinded, randomized clinical trial. Am Heart J. 2020;221:114–24.
80. Constantin MU, Alexandru I. The role of sodium in the body. Balneo-Res J. 2011;2(1):70–4.
81. Frisoli TM, Schmieder RE, Grodzicki T, Messerli FH. Salt and hypertension: is salt dietary reduction worth the effort? Am J Med. 2012;125(5):433–9.
82. Pääkkö TJW, Perkiömäki JS, Silaste ML, Bloigu R, Huikuri HV, Antero Kesäniemi Y, Ukkola OH. Dietary sodium intake is associated with long-term risk of new-onset atrial fibrillation. Ann Med. 2018;50(8):694–703.
83. Cavusoglu Y, Kaya H, Eraslan S, Yilmaz MB. Hyponatremia is associated with occurrence of atrial fibrillation in outpatients with heart failure and reduced ejection fraction. Hellenic J Cardiol. 2019;60(2):117–21.
84. Lu YY, Cheng CC, Chen YC, Lin YK, Chen SA, Chen YJ. Electrolyte disturbances differentially regulate sinoatrial node and pulmonary vein electrical activity: a contribution to hypokalemia-or hyponatremia-induced atrial fibrillation. Heart Rhythm. 2016;13(3):781–8.
85. Takase H, Machii M, Nonaka D, Ohno K, Sugiura T, Ohte N, Dohi Y. P1899 Relationship between dietary salt intake and atrial fibrillation in the general population. Eur Heart J. 2018. https://doi.org/10.1093/eurheartj/ehy565.P1899.
86. Can C, Gülaçti U, Kurtoglu E, Çelik A, Lök U, Topacoglu H. The relationship between serum sodium concentration and atrial fibrillation among adult patients in emergency department settings. Euras J Emerg Med. 2014;13(3):131.
87. Levi AJ, Dalton GR, Hancox JC, Mitcheson JS, Issberner JON, Bates JA, Evans SJ, Howarth FC, Hobai IA, Jones JV. Role of intracellular sodium overload in the genesis of cardiac arrhythmias. J Cardiovasc Electrophysiol. 1997;8(6):700–21.
88. Dudenbostel T, Matanes F, Salzer G, Mayfield J, Siddiqui M. Association of low sodium-potassium ratio with atrial fibrillation in patients with primary aldosteronism. J Hypertens. 2019;37: e55.
89. King DE, Dickerson LM, Sackier JM. Acute management of atrial fibrillation: part I. Rate and rhythm control. Am Family Phys. 2002;66(2):249.
90. Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. Circulation. 2012;125(2):381–9.
91. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H. Guidelines for the management of atrial fibrillation (vol 12, pg 1360, 2010). Europace. 2011;13(7):1058–1058.
92. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huther ML. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the cardiac arrhythmia suppression trial. N Engl J Med. 1991;324(12):781–8.
93. Huang DT, Monahan KM, Zimetbaum P, Papageorgiou P, Mepstein L, Josephson ME. Hybrid pharmacologic and ablative therapy: a novel and effective approach for the management of atrial fibrillation. J Cardiovasc Electrophysiol. 1998;9(5):462–9.
94. Nabar A, Rodriguez LM, Timmermans C, Van Mechelen R, Wellens HJJ. Class IC antiarrhythmic drug induced atrial flutter: electrocardiographic and electrophysiological findings and their importance for long term outcome after right atrial isthmus ablation. Heart. 2001;85(4):424–9.

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