Hypothesis: Potassium sparing by angiotensin and aldosterone inhibitors preserves skeletal muscle mass in chronic heart failure

Lara Zwakman-Hessels¹, Miriam Zeillemaker-Hoekstra² & Maarten W. Nijsten¹*

¹Department of Critical Care, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9700 RB, Groningen, The Netherlands, ²Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9700 RB, Groningen, The Netherlands

Abstract

Background Cachexia complicates many chronic diseases. In chronic or congestive heart failure (CHF), cachexia independently contributes to decreased survival. Although diuretics have long been part of standard treatment of CHF, the addition of angiotensin and aldosterone antagonists to the standard treatment regimen has considerably improved the outcome of CHF. Both loop diuretics and the up-regulation of the renin–angiotensin–aldosterone system caused by CHF induce loss of total body potassium (TBK).

Hypothesis In addition to the causal association of loss of muscle mass with loss of TBK, we propose that the reverse mechanism also exists. The known beneficial effects of angiotensin and aldosterone inhibition may partly result from preserved TBK with consequent muscle mass preservation.

Conclusion We propose that monitoring of muscle mass, potassium balances, and TBK should be included in future CHF studies to verify this hypothesis and allow further optimization of therapy.

Keywords Potassium; Chronic heart failure; Muscle mass; Cachexia; Total body potassium

Introduction

Cachexia is a serious complication of many chronic diseases, such as cancer, liver cirrhosis, and heart failure.⁴ The loss of skeletal muscle in patients with chronic or congestive heart failure (CHF) is related to impaired survival, independent of other factors.⁴ As CHF is currently the third most common chronic co-morbidity, cachexia constitutes a public health issue.⁵ Prevention of the loss of muscle mass in CHF might improve outcome. We propose a new hypothesis considering an important role of the loss of potassium in cardiac cachexia through both the activation of the renin–angiotensin–aldosterone system (RAAS) and the use of loop diuretics and the potential protective effect of angiotensin and aldosterone inhibition on skeletal muscle mass.

Chronic heart failure

CHF remains one of the most common, disabling and deadly chronic diseases, with a quality of life lower than that of many other chronic diseases.⁶ The pathophysiology of CHF is complex and multifactorial, with interaction of immune, metabolic, and neurohormonal factors, which eventually facilitate a chronic catabolic state.⁷ The impaired cardiac function in CHF leads to neurohormonal activation through the sympathetic nervous system, RAAS, and the natriuretic peptide system.⁸, ⁹ The up-regulation of both epinephrine and norepinephrine causes a catabolic shift, leading to a higher resting energy expenditure in CHF patients. However, up-regulation of the RAAS in CHF has long been seen as the inducer of cachexia, as both angiotensin II and aldosterone
are associated with muscle wasting\(^6\) (Figure 1). Currently, it is thought that angiotensin II causes muscle wasting through multiple mechanisms, such as increased oxidative stress, increased protein breakdown, reduced appetite, impaired energy balance, and inhibition of satellite cell function and muscle regeneration.\(^3\) Aldosterone is associated with both cardiac and skeletal muscle loss and myocyte apoptosis.\(^6\) It also promotes the retention of sodium, loss of potassium and magnesium, sympathetic activation, parasympathetic inhibition, and vascular and myocardial fibrosis.\(^9\)

The management of CHF has greatly improved over the last decades. Established components of CHF treatment are loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). Loop diuretics are used to prevent fluid and sodium overload in CHF patients. Both ACE inhibitors and ARBs reduce angiotensin II and therefore lead to improvement in symptoms and prolonged survival in CHF patients.\(^6\) In patients with symptomatic heart failure, addition of the MRA spironolactone leads to an additional reduction of both morbidity and mortality.\(^7\)

**Total body potassium**

From an evolutionary point of view, humans have never been confronted with potassium-scarce diets. Therefore, very limited mechanisms exist to preserve potassium, in contrast to sodium.

Potassium is the major cation of the intracellular compartment. A large part of the total body potassium (TBK) resides in skeletal muscle, and radionuclear TBK quantification can be used to measure muscle mass.\(^8\) Cachexia thus logically leads to a reduction in TBK,\(^9,\,10\) which has been observed in other cachectic patient groups. During critical illness, a reduction in both the intracellular volume and TBK is seen.\(^11,\,12\)

Heart failure itself is associated with a loss of TBK\(^13\) (Figure 1). This is not only because of the loss of muscle mass but also because of intracellular potassium depletion,\(^14\) underscoring the constant stress that the intracellular compartment is exposed to in this situation. The potassium depletion in CHF is partly explained by up-regulation of the RAAS and therefore increased aldosterone secretion. This loss can be exacerbated by the treatment of CHF with diuretics.\(^9\) Several studies have shown that long-term treatment with conventional loop diuretics such as furosemide and bumetanide leads to a decrease in intracellular potassium concentration in skeletal muscle cells.\(^15,\,16\)

An important part of resting energy expenditure is devoted to the maintenance of Na\(^+/\)K\(^+\) gradients.\(^17\) The constant extra work to maintain these gradients, resulting from mild hypokalaemia caused by CHF itself and diuretics, will place additional energetic demands on the already often poorly perfused skeletal muscle and other tissues. Because it is essential that the intracellular potassium concentration be held above a minimal concentration, a cell only has one strategy left when faced with ongoing potassium loss to the extracellular space, namely, to reduce its volume or to go into apoptosis.

A key part of the CHF treatment is targeted against the up-regulation of the RAAS and thus may be beneficial in the prevention of loss of TBK and muscle mass (Figure 1). Use of ACE inhibitors is associated with a reduction in weight loss in cachectic CHF patients and delays the development of cachexia by 8 months.\(^1,\,18\) ARBs might also have a favourable effect on the cachectic effects of RAAS, as found in different mouse models of myopathy that demonstrated increased muscle strength and muscle regenerative ability after ARB treatment.\(^18\)

Several studies show that in both CHF and liver cirrhosis patients, when spironolactone is added to conventional treatment this results in a rise in intracellular potassium, even when it was first depleted.\(^2,\,19\) Intracellular potassium even

---

**Figure 1** Schematic depiction of the proposed hypothesis. CHF induces up-regulation of the RAAS, hereby increasing the loss of TBK. CHF treatment with diuretics further aggravates this loss. The loss of TBK leads to loss of muscle mass and vice versa. We propose that part of the beneficial effect of angiotensin and aldosterone inhibition results from a preservation of TBK and consequently muscle mass. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, chronic (or congestive) heart failure; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; TBK, total body potassium.
increased to a concentration similar to that of healthy controls.\textsuperscript{2}

Furthermore, it has been shown that spironolactone increases exercise tolerance in CHF patients, also suggesting that this increase in intracellular potassium might impact on the quality of muscle.\textsuperscript{20} An increase in serum creatinine is often observed after addition of an MRA, and this only underscores the beneficial effect of angiotensin and aldosterone inhibition on skeletal muscle.\textsuperscript{19}

Preservation of total body potassium and prevention of cachexia

CHF is accompanied by (intracellular) potassium depletion. Interestingly, nobody has linked this potassium depletion and the success of the angiotensin and aldosterone inhibitors in the treatment of CHF. The beneficial effect of MRAs and the already aldosterone-blocking ACE inhibitors or ARBs may very well be dual: in addition to further counteracting aldosterone , this cocktail may also be muscle sparing (Figure 1). We postulate that the persistent loss of intracellular potassium leads to loss of muscle mass in CHF patients and vice versa.

Testing the hypothesis

Although several studies have shown that the potassium concentration rises in skeletal muscle after starting MRAs, no study has yet directly demonstrated the relation between intracellular potassium loss and muscle wasting.

It is difficult to assess TBK. The gold standard for TBK is \textsuperscript{40}K scintigraphy, which is a cumbersome and expensive method. However, the absolute value of TBK is not necessarily needed to determine alterations in TBK. Potassium balances might be a much easier and reliable way to assess changes in TBK.\textsuperscript{20, 12} Monitoring the amount of muscle loss and potassium balances in CHF patients would provide us with more information regarding the association between potassium loss and muscle wasting. The increased resting energy expenditure that is needed in CHF patients to maintain the Na⁺/K⁺ gradient might be assessed with indirect calorimetry or fluorodeoxyglucose positron emission tomography scanning.

However, to our knowledge, no such studies have been conducted in potassium-depleted patients. Because the effect of angiotensin and aldosterone inhibition has not been directly tested on skeletal muscle preservation and function, this should also be further studied.

Implications

This hypothesis provides an additional explanation of the beneficial effect of angiotensin and aldosterone inhibitors on muscle mass. ACE inhibitors, ARBs, and MRAs might also be beneficial in other patient groups, for example, other chronic diseases leading to cachexia, older patients, and critically ill patients. As our society ages, the prevalence of chronic diseases will rise. This makes cachexia a major public health problem, requiring treatments that minimize muscle wasting.

Monitoring potassium balances is an easy and reliable way to monitor skeletal muscle loss and thereby the possible effectiveness of treatment. We therefore propose that future CHF studies should address potassium balances together with monitoring of muscle mass.

Acknowledgement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle.\textsuperscript{21}

Conflict of interest

Lara Zwakman-Hessels, Miriam Zeillemaker-Hoekstra, and Maarten W. Nijsten declare that they have no competing interests.

Funding

There was no external funding for this work.

References

1. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;361:1077–1083.
2. Aagaard NK, Andersen H, Vilstrup H, Clausen T, Jakobsen J, Dørup I. Muscle strength, Na,K-pumps, magnesium and potassium in patients with alcoholic liver cirrhosis—relation to spironolactone. J Intern Med 2002;252:56–63.
3. Loncar G, Springer J, Anker M, Doehner W, Lainscak M. Cardiac cachexia: hic et nunc. J Cachexia Sarcopenia Muscle 2016;7:235–260.

JCSM Rapid Communications 2020; 3: 77–80
DOI: 10.1002/rco.17
4. McMurray JJV, Stewart S. The burden of heart failure. *Eur Heart J Suppl* 2002;4: D50–D58.
5. Anker SD, Sharma R. The syndrome of cardiac cachexia. *Int J Cardiol* 2002;85:51–66.
6. Burniston JG, Saini A, Tan LB, Goldspink DF. Aldosterone induces myocyte apoptosis in the heart and skeletal muscles of rats in vivo. *J Mol Cell Cardiol* 2005;39:395–399.
7. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–717.
8. Heymsfield SB, Gallagher D, Visser M, Nunez C, Wang ZM. Measurement of skeletal muscle: laboratory and epidemiological methods. *J Gerontol A Biol Sci Med Sci* 1995;50:23–29.
9. Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR, Hamer J.Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. *Br Heart J* 1979;42:316–325.
10. Patrick J. Assessment of body potassium stores. *Kidney Int* 1977;11:476–490.
11. Finn PJ, Plank LD, Clark MA, Connolly AB, Hill GL. Progressive cellular dehydration and proteolysis in critically ill patients. *Lancet* 1996;347:654–656.
12. Hessels L, Oude Lansink A, Renes MH, van der Horst IC, Hoekstra M, Touw DJ, et al. Postoperative fluid retention after heart surgery is accompanied by a strongly positive sodium balance and a negative potassium balance. *Physiol Rep* 2016;4:e12807.
13. Nicholls MN. Interaction of diuretics and electrolytes in congestive heart failure. *Am J Cardiol* 1990;65:17E–21E.
14. Cox JR, Horrocks P, Speight CJ, Pearson RE, Hobson N. Potassium and sodium distribution in cardiac failure. *Clin Sci* 1971;41:55–61.
15. Borchgrevink PC. Tissue electrolyte changes induced by high doses of diuretics in rats. *Pharmacol Toxicol* 1987;60:77–80.
16. Buggey J, Mentz RJ, Pitt B, Eisenstein EL, Anstrom KJ, Velazquez EJ, et al. A reappraisal of loop diuretic choice in heart failure patients. *Am Heart J* 2015;169:323–333.
17. Pirkmajer SJ, Chibalin AV. Na,K-ATPase regulation in skeletal muscle. *Am J Physiol Endocrinol Metab* 2016;311:E1–E31.
18. Yoshida T, Tabony AM, Galves S, Mitch WE, Higashi Y, Sukhanov S, et al. Molecular mechanisms and signaling pathways of angiotensin II-induced muscle wasting: potential therapeutic targets for cardiac cachexia. *Int J Biochem Cell Biol* 2013;45:2322–2332.
19. Dyckner T, Widman L. Effects of spironolactone on serum and muscle electrolytes in patients on long-term diuretic therapy for congestive heart failure and/or arterial hypertension. *Eur J Clin Pharmacol* 1986;30:535–540.
20. Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 2002;40:304–310.
21. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;8:1081–1083.