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Opinion Article

The use of L-arginine in heart failure: An educational article and expert opinion

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Abstract

Diuretics especially loop diuretics have been considered the mainstay of the treatment of chronic heart failure for decades. In 2007, Jerie reviewed the literature and emphasized the strong evidence suggesting that digoxin can reduce the hospitalizations and mortality rate in patients with chronic heart failure. Jerie suggested that digoxin should be used before adding ACE-inhibitors, angiotensin receptor blockers, and using aggressive diuretic therapy which can be complicated by electrolyte abnormalities, when treating chronic heart failure.

The use of health supplements in the treatment of variety of cardiovascular and non- cardiovascular chronic disorders has been increasingly suggested. Arginine is an amino acid that is important for being a precursor for the production of nitric oxide, and for playing a role in the regulation of blood pressure, and it has been increasingly used as a health supplement for having beneficial effects in a variety of conditions.

L-arginine has been recognized as safe (GRAS-status) when taken in an oral dose of up to 20 g daily. The aim of this paper is to provide an overview of the use of arginine in heart failure.

Conclusion and expert opinion: Heart failure is generally associated with significant morbidity, poor quality of life, and mortality. The addition of a safe therapeutic supplement to the already known therapeutic armamentarium is desirable. The current evidence-based opinion suggests that because supplementation of amino acid such as L-arginine is safe and can be effective when used appropriately in patients with heart failure, it is important for physicians treating patients with hear failure to be aware of such potentially important adjunctive therapy.

Keywords: L-arginine, heart failure, educational article, expert opinion.endothelium; rats; cerebral ischemia; alcohol

Introduction

Diuretics especially loop diuretics have been considered the mainstay of therapy of chronic heart failure for decades [1-4].

In 2007, Jerie reviewed the literature and emphasized the strong evidence suggesting that digoxin can reduce the hospitalizations and mortality rate in patients with chronic heart failure. Jerie suggested that digoxin should be used before adding ACE-inhibitors, angiotensin receptor blockers, and using aggressive diuretic therapy which can be complicated by electrolyte abnormalities when treating chronic heart failure [4].

In 2013, Hu et al conducted a systematic review of the literature and a meta-analysis which included 8 studies involving 3929 patients with chronic heart failure. They found that the addition of an aldosterone antagonist such as spironolactone in patients with chronic heart failure can improve heart function and left vermicular reverse remodeling and reduce mortality and hospitalization because of heart failure [5].

In 2020, Abraham et al conducted a systematic review of the literature and a meta-analysis which included 19 studies (9 randomized controlled studies and 10 observational studies) involving 19280 patients. Torsemide was associated with much more improvement in functional status of patients with heart failure than furosemide, less risk of hospitalization because of to heart failure, and less cardiac mortality than furosemide. The reported side effects of torsemide and furosemide were similar [6].

The use of health supplements in the prevention and treatment of variety of cardiovascular and non cardiovascular chronic disorders has been increasingly suggested [7-12].

Arginine is an amino acid that is important for being a precursor for the production of nitric oxide and for playing a role in the regulation of blood pressure, and it has been increasingly used as a health supplement for having beneficial effects in a variety of conditions. L-arginine has been recognized as safe (GRAS-status) when taken in an oral dose of up to 20 g daily [13-14].

In 1886, Ernst Schulze **(**Figure-1A) and Ernst Steiger reported the isolation of arginine from yellow lupin seedlings and they called it arginine after árgyros, a Greek word means silver, because of the silver-white color of

arginine nitrate crystals [15]. In 1897, Ernst Schulze and Ernst Winterstein (Figure-1B) clarified the structure of arginine, and in 1899, they synthesized it from ornithine and cyanamide [16-17].

Arginine is the precursor of nitric oxide which is an important contributor to microvascular vasodilation and to the reduction of atherosclerosis. Therefore, oral L-arginine has been emerging as a new effective therapeutic approach for reducing blood through improving endothelial function [14].

In 1995, Koifman et al reported a study which included 12 patients with ischemic congestive heart failure and left ventricular ejection fraction below 35%.

Figure-1A: Ernst Schulze (July 31, 1840- June 15, 1912), a German chemist who discovered several amino acids

Figure-1B: Ernst Winterstein (June 17, 1865-July 4, 1949), a chemist from Switzerland

The patients were treated with L-arginine, 20 grams given by intravenous infusion over one hour. Treatment was associated with a considerable improvement in stroke volume and cardiac output without changing heart rate. Treatment was also associated with significant lowering of blood pressure and systemic vascular resistance. One hour after treatment, blood pressure, stroke volume, cardiac output and systemic vascular resistance were similar to the baseline values. The beneficial hemodynamic effects of L-arginine infusion were attributed to higher production of nitric oxide [18].

In 1996, Rector et al from the United States reported a placebo-controlled study which included 15 patients with heart failure who received oral L-arginine (5.6 to 12.6 grams) daily for six weeks.

L-arginine supplementation increased the distance during a 6-minute walk, and considerably increased forearm blood flow during forearm exercise. L-arginine supplementation also improved arterial compliance and reduced circulating levels of endothelin [19].

In 2000, Kaye et al from Australia reported a study which showed in vivo and in vitro evidence of impaired arginine transport in patients with heart failure suggesting that L arginine supplementation can have restorative effects on the vascular function in patients with heart failure [20].

In 2002, Kaye and from Australia colleagues reported a study which included seven patients who had moderate to severe congestive heart failure and nine healthy individuals (Control). The study showed that myocardial uptake of L-arginine in patients with congestive heart failure was markedly less than in the controls [21].

In 2004, Bednarz et al from Poland emphasized that endothelial dysfunction may be a factor in impaired vasodilatation during exercise and contributes to reduced exercise capacity in patients with congestive heart failure.

Bednarz et al reported a placebo-controlled study which included 21 patients with stable congestive heart failure treated with either oral L-arginine (9 grams) daily or placebo for one week. L-arginine supplementation was associated with prolongation of exercise duration. The beneficial effect of L-arginine was attributed to nitric oxide-induced vasodilatation [22].

In 2006, Kendler emphasized that conditional amino acids such as L-arginine are produced by the body in sufficient amounts in normal circumstances. However, these amino acids may not be produced in adequate amounts in cardiovascular disorders. Because supplementation of amino acid such as L-arginine is safe and can be effective when used appropriately. Kendler recommended that healthcare professionals have to be knowledgeable of such potentially important additions that can improve the management of cardiovascular disorders [23].

In 2009, Fontanive et al from Italy reported a placebo-controlled study which included sixty-eight patients who had mild-to-moderate systolic heart failure and left ventricle ejection fraction of 45% or less. Thirty-seven patients received oral L-arginine 6 grams in 3 divided doses daily, and thirty-one patients received placebo for three months. L-arginine supplementation was associated with improved quality of life [24].

In 2010, Orozco-Gutiérrez et al from Mexico reported a study which included thirty patients with heart failure patients associated with preserved ejection fraction. Fifteen patients received L-arginine, 8 grams daily, and 15 patients received citrulline malate, 3 grams daily for 2 months. Both of L-arginine and citrulline supplementation was associated with improvement in right ventricular function through increasing right ventricle ejection fraction [25].

In 2021, Salmani et al reported a study which included fifty patients with ischemic heart failure. Patients received either L-arginine 3 grams daily or placebo for 10 weeks. L-arginine supplementation was associated with considerable improvements in left ventricular and diastolic dysfunctions and improved ejection fraction. L-arginine supplementation was also associated with marked improvement in the quality of life [26].

Conclusion and expert opinion

Heart failure is generally associated with significant morbidity, poor quality of life, and mortality. The addition of a safe therapeutic supplement to the already known therapeutic armamentarium is desirable. The current evidence-based opinion suggests that because supplementation of amino acid such as L-arginine is safe and can be effective when used appropriately in patients with heart failure, it is important for physicians treating patients with hear failure to be aware of such potentially important adjunctive therapy.

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The author has the copyright of the sketches in this paper.

Conflict of interest: None.

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