

Midodrine and Pyridostigmine; Novelties in Heart Failure Therapy

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ABSTRACT

Objectives: Providing a comprehensive review of the beneficial effects of Midodrine and Pyridostigmine in heart failure.

Background: Heart failure is a leading cause of mortality, and morbidity. Applying the standard medical therapy is often limited by developing side effects. This study explores the role of Midodrine in optimizing heart failure therapy, and describes the role of Pyridostigmine as a novel agent in the treatment of heart failure. **Methods:** A 16 years search was conducted through PubMed, using the search terms Midodrine and Pyridostigmine each in association with cardiac failure, congestive heart failure, heart failure, or other related terms. Articles through December 2015 were used. **Results and discussion:** Using Midodrine in hypotensive patients with heart failure resulted in a twofold increase in the number of patients on optimal medical therapy, increase in ejection fraction, decrease in hospitalization days, and symptomatic improvement. Pyridostigmine use in heart failure was associated with beneficial effects in cardiac remodeling and with improvement in ejection fraction in animal models, and with better cardiac exercise response profile in humans. **Conclusion:** Pyridostigmine carry potential benefits in heart failure therapy and Midodrine can be beneficial in patients with heart failure and hypotension. This needs to be verified in larger studies.

Key words: Heart failure, Cardiac failure, CHF, Midodrine, Pyridostigmine.

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INTRODUCTION

Heart failure is emerging as one of the major medical problems in the United States, affecting 5.1 million US individuals according to the last statistical update by the American Heart Association.¹ Mortality from heart failure exacerbations remains high despite available therapy.² In addition, physical symptoms of heart failure were shown to be the most important predictor of health related quality of life.³ Application of medical therapy is often limited by medication side effects, leading to a decreased number of patients on optimal medical therapy.⁴ Limitation in the available therapy is driving scientists and clinicians to explore new treatment modalities and to find ways to optimize current treatment options. In this review, we focus on 2 drugs that may carry potential benefit for patients with heart failure. This paper will discuss the role of Midodrine - alpha one agonist -, and Pyridostigmine - acetylcholine esterase inhibitor - in heart failure therapy.^{5,6} To our own knowledge, this article is the first to provide a comprehensive review of the beneficial effects of the use of Midodrine and Pyridostigmine in heart failure therapy. Data from *in vitro* studies, studies involving animal models, along with data from human studies will be presented.

METHODS

A 16 years search was conducted through PubMed, using the search terms Midodrine, Pyridostigmine, each in association with cardiac failure, congestive heart failure, heart failure, or other related terms. Articles through December 2015 were isolated. The identified literature was further evaluated for original studies and reports. Articles were then assessed for beneficial effects presented. Data from studies *in vitro*, animal models, and human studies and reports was reported. A total of 9 articles were reviewed.

RESULTS AND DISCUSSION

Midodrine

Application of heart failure therapy is often limited by certain contraindications and by the development of medication side effects.^{4-7,8} Hypotension was shown to be the cause of 28% of treatment failure in patients with systolic heart failure.⁴ In a separate study, Lisinopril use was associated with hypotension or dizziness in 12.8% of patients when given in high dose and in 9% of patients when given in low dose.⁹ On the other hand, dizziness 41% and hypotension 28% were reported in patients with systolic heart failure on beta blocker therapy.⁴

Midodrine is a prodrug metabolized by the liver into Desglymidodrine, an active metabolite with selective alpha 1 receptor agonist properties.¹⁰ Midodrine is an oral agent that acts peripherally leading to increase in blood pressure.⁵ This agent has been used for the treatment of symptomatic hypotension in several medical conditions.⁶ The potential role of Midodrine in the treatment of heart failure has been examined in two separate studies. Patients with end stage renal disease and symptomatic New York Heart Association class III-IV heart failure, all with symptomatic hypotension during dialysis and with previous hospital admissions for volume overload were included in an observational, small size study by Bregman.¹² When using Midodrine, the lowest mean arterial pressure during dialysis, along with the mean arterial pressure after dialysis were significantly improved. This was accompanied by a subjective improvement in dyspnea and orthopnea in all five patients studied, and by a transition to "edema free" state in four out of the five patients. In a separate observational study, Zakir and colleagues showed that in ten patients with systolic heart failure and symptomatic hypotension interfering with optimizing medical therapy, the use of Midodrine was associated with a significant increase in the percentage of patients on optimal medical therapy.¹³ At the end of the study 57.5% of patients were on optimal dose of ACEI/ARB vs 20% initially, 75% compared to 37.5% of patients were on optimal dose beta blocker, and 95% compared to 43.7% of patients were on optimal Spironolactone/Eplerenone therapy. (Figure 1) The use

of Midodrine was further associated with an improvement in left ventricular ejection fraction. Furthermore, patients on Midodrine had fewer hospital admissions and fewer total hospital days (150 vs 58) within a six month period. Lastly, in a separate article, Midodrine was reported to be successfully used in the treatment of hypotension stemming from myocardial stunning post myocardial infarction.¹⁴ Table 1 summarizes the findings of the studies on Midodrine in heart failure patients. (Table 1) The known side effects of Midodrine include piloerection, supine hypertension, and urinary disturbances among others.⁵ None of the reviewed studies mentions the presence of any of these side effects in the study groups, although the groups were rather small and it is likely that if used in a larger population some of these side effects would be noted.

Pyridostigmine

Decrease in heart rate variability was shown to be associated with increased mortality in patients with chronic heart failure.¹⁵ Furthermore, heart rate recovery after exercise is an independent predictor of mortality/hospitalization in patients with heart failure.¹⁶ Chemoreceptor hypersensitivity was shown to be another independent predictor of mortality in patients with heart failure.¹⁷ None of the studies involving pro-cholinergic agents in the treatment of heart failure have reached clinical application yet.¹⁸⁻²²

Pyridostigmine is a reversible acetylcholine esterase inhibitor, it augments the effect of the parasympathetic system.⁶⁻²⁰ It is currently used in the treatment of myasthenia gravis.²³ Several efforts to study the effect of Pyridostigmine in animal models of heart failure have been made. In a study by Lara *et al.* genetically modified mice with reduced expression of the vesicular acetylcholine transporter developed left ventricular failure.²¹ They also experienced significant cardiac remodeling that was found to be a result of activation of fetal gene program. However, when given Pyridostigmine, mice experienced improvement in left ventricular systolic tension and left ventricular fractional shortening. Moreover, the use of Pyridostigmine was associated with a decrease in left ventricular cross sectional area and in left ventricular concentric hypertrophy evaluated at six months of treatment. B-type natriuretic peptide, atrial natriuretic factor, and beta myosin heavy chain levels were high in the genetically modified mice, and went back to normal with 2 weeks of treatment with Pyridostigmine. In another animal study by Lataro *et al.*, the use of Pyridostigmine in heart failure models was associated with decrease in myocyte diameter, increase in stroke volume, cardiac output and contractility.²⁰ At 4 weeks of treatment, Pyridostigmine group had an EF of 25% compared to 15% in the control group. Pyridostigmine group had a higher level of vascular endothelial growth factor expression (suggesting angiogenesis) and a higher collagen density in cardiac myocytes. Sabino and his team showed that Pyridostigmine decreased baroreflex to bradycardia, preventing impairment of baroreflex sensitivity in rats with heart failure due to coronary ischemia.²² In the same study, the increase in the heart rate of rats with heart failure in response to hypercapnia was reduced by the use of Pyridostigmine, and the increase in pulmonary ventilation in response to hypoxia was also decreased in Pyridostigmine group. In this study, Pyridostigmine did not increase mean arterial pressure and it did not increase baseline pulmonary ventilation.

Several smaller scale studies have been conducted in humans as well. In one study involving 23 stable patients with heart failure with reduced ejection fraction, Pyridostigmine was associated with 65% reduction in the frequency of premature ventricular complexes, without a change in the frequency of ventricular tachycardia.²⁴ Pyridostigmine group had a positive change in short term heart rate variability indices, thus reflecting an increase in short term heart rate variability. There was no change in left ventricle dimension in the treatment group, but these patients had an increase in E to A ratio and an increase in peak velocity. In a separate

study, Serra and his colleagues showed that Pyridostigmine blunted the increase in heart rate in response to exercise in heart failure patients up to 60% of maximum tolerated exercise.²⁵ There was an increase in pulse pressure at peak exercise but without a change in the peak heart rate. Moreover, there was no change in maximum exercise capacity, hinting towards the neutrality of Pyridostigmine regarding functional capacity in patients with heart failure. In one study involving 20 patients with heart failure with a mean EF of 24%, Pyridostigmine was associated with improved heart rate recovery at one minute after exercise termination, without any difference at 3 minutes, again without affecting exercise performance.²⁶ Table 2 summarizes the findings of the studies on Pyridostigmine in heart failure. (Table 2) The reviewed articles concluded that Pyridostigmine was well tolerated in patients with heart failure. The absence of reported side effects is likely due to the small number of patients and the small duration of these studies.

Table 1: Summary of the effects of Midodrine on patients with heart failure

Author (year)	Title	Findings
Bergman (2009)	Hemodialysis in hypotensive heart failure using Midodrine	Mean arterial pressure during dialysis improved with Midodrine therapy
Zakir <i>et al.</i> (2009)	The use of Midodrine in patients with advanced heart failure	Use of Midodrine enabled usage of optimal medical therapy in hypotensive heart failure
Sharma <i>et al.</i> (2005)	Successful treatment of hypotension associated with stunned myocardium with oral Midodrine therapy	Midodrine can substitute IV inotropes in treatment of hypotension from myocardial stunning

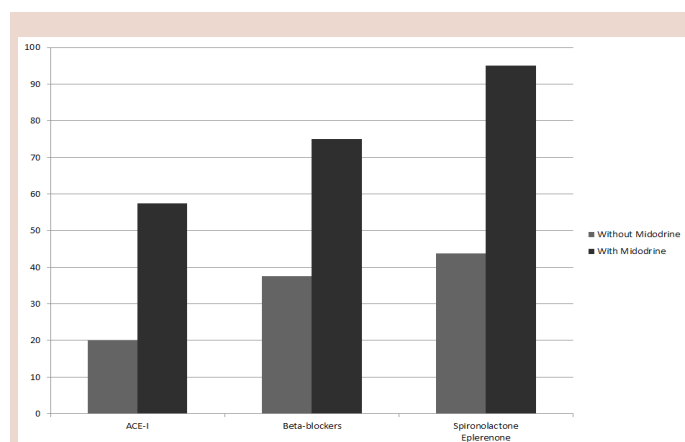


Figure 1: Percentage of patients on optimal dose of Angiotensin Converting Enzyme Inhibitor (ACE-I) (mg), beta-blocker (mg) or mineralocorticoid receptor antagonist (mg) in patients with congestive heart failure and hypotension with and without addition of midodrine to treatment (chart made based on data by Zakir *et al.*)

Table 2: Summary on the effect of Pyridostigmine in heart failure study groups

Author (year)	Title	Findings
Lara <i>et al.</i> (2010)	Dysautonomia due to reduced cholinergic neurotransmission causes cardiac remodeling and heart failure	The use of Pyridostigmine in genetically modified mice with left ventricular failure resulted in improved cardiac remodeling
Lataro <i>et al.</i> (2013)	Increase in parasympathetic tone by Pyridostigmine prevents ventricular dysfunction during the onset of heart failure	Pyridostigmine use in heart failure models was associated with decrease in myocyte diameter, increase in stroke volume, cardiac output and contractility
Sabino <i>et al.</i> (2013)	Parasympathetic activation by Pyridostigmine on chemoreflex sensitivity in heart-failure rats	In rats with heart failure due to coronary ischemia, Pyridostigmine decreased baroreflex to bradycardia and blunted the increase in the heart rate in response to hypercapnia
Behling <i>et al.</i> (2003)	Cholinergic stimulation with Pyridostigmine reduces ventricular arrhythmia and enhances heart rate variability in heart failure	Pyridostigmine reduced the frequency of premature ventricular complexes and improved short term heart rate variability indices in patients with heart failure
Serra <i>et al.</i> (2009)	Cholinergic stimulation improves autonomic and hemodynamic profile during dynamic exercise in patients with heart failure	In heart failure patients, Pyridostigmine blunted the increase in heart rate in response to exercise up to 60% of maximum tolerated exercise without a change in heart rate at peak exercise tolerance
Androne <i>et al.</i> (2003)	Acetylcholinesterase inhibition with Pyridostigmine improves heart rate recovery after maximal exercise in patients with chronic heart failure	In patients with reduced ejection fraction, Pyridostigmine was associated with improved heart rate recovery at one minute after exercise termination without any effect on exercise performance

CONCLUSION

The agents that were reviewed in this paper, Midodrine and Pyridostigmine may find application as adjuvant therapies in the treatment of particular subgroups of patients with heart failure. It is known that the benefits of standard medical treatment with ACEI/ARB, beta-blockers and aldosterone antagonists stem not only from their known effects on afterload reduction, but also from effects on myocardial remodeling which drives the progression of heart failure. As stated above, optimization of these therapies by up-titration to a target dose was shown to have additional benefits in a clinical setting, although side effects (mainly hypotension) limit the use of target doses in all patients. Although using Midodrine to eliminate hypotension and optimize medical therapy in heart failure patients carries a great potential towards better effects that may include survival, it has only been studied in a small cohort of 10 patients. There are no large placebo-controlled randomized studies to date that examine this issue. Pyridostigmine in human heart failure was so far associated with better cardiac exercise response profile, but the beneficial effects on remodeling and cardiac function which were demonstrated in animal studies were not thoroughly looked at in human studies. The two reviewed agents could be beneficial in treatment of heart failure, but require large randomized studies to examine their effects.

Clinical perspectives

As mentioned earlier, application of the standard therapy for heart failure is often limited by medication side effect. And despite available therapy, mortality from heart failure remains to be high. This review highlights the role of Midodrine in increasing the percentage of patients on optimal medical therapy. This review further describes the benefits of Pyridostigmine observed on cardiac remodeling and cardiac function in animal models and in limited human studies, thus hinting towards their possible role in the future of heart failure therapy.

Translational outlook

The role of Midodrine in optimizing heart failure therapy needs to be explored in a randomized controlled trial involving adequate number of

patients, looking into long term therapy effects to determine if the use of Midodrine is associated with better mortality, hospitalization rates, or other significant outcomes. On the other hand, while Pyridostigmine does improve cardiac remodeling and cardiac function in animal models, this needs to be explored in humans. Whether or not Pyridostigmine will have similar effects on human hearts, and whether or not these benefits will outweigh the risks associated with the dose used needs to be determined.

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CONFLICT OF INTEREST

All authors declared no conflict of interest.

ABBREVIATION USED

ACEI: Angiotensin converting enzyme inhibitor; **ARB:** Angiotensin receptor blocker; **EF:** Ejection Fraction.

REFERENCES

- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Baha MJ, *et al.* Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28–292.
- Follath F, Yilmaz MB, Delgado JF, Parissis JT, Porcher R, Gayat E, *et al.* Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF). *Intensive Care Med*. 2011;37(4):619–26.
- Heo S, Doering LV, Widener J, Moser DK. Predictors and effect of physical symptom status on health-related quality of life in patients with heart failure. *Am J Crit Care Off Publ Am Assoc Crit-Care Nurses*. 2008;17(2):124–32.
- Butler J, Khadim G, Belue R, Chomsky D, Dittus RS, Griffin M, *et al.* Tolerability to beta-blocker therapy among heart failure patients in clinical practice. *J Card Fail*. 2003;9(3):203–9.
- McTavish D, Goa KL. Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorder.

- ders. *Drugs*. 1989;38(5):757–77.
6. Aquilonius SM, Hartvig P. Clinical pharmacokinetics of cholinesterase inhibitors. *Clin Pharmacokinet*. 1986;11(3):236–49.
 7. Kuhn M. Angiotensin-converting enzyme inhibitors. *AACN Clin Issues Crit Care Nurs*. 1992;3(2):461–71.
 8. Naik SD, Freudenberger RS. Beta-blocker contraindications: are there patients or situations where use is inappropriate? *Curr Heart Fail Rep*. 2007;4(2):93–8.
 9. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, *et al.* Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100(23):2312–8.
 10. Cruz DN. Midodrine: a selective alpha-adrenergic agonist for orthostatic hypotension and dialysis hypotension. *Expert Opin Pharmacother*. 2000;1(4):835–40.
 11. Mansourati J. [Orthostatic hypotension: implications for the treatment of cardiovascular diseases]. *Presse Médicale Paris Fr* 1983. 2012;41(11):1111–5.
 12. Bergman SM. Hemodialysis in hypotensive heart failure using midodrine. *Am J Med Sci*. 2009;338(6):470–3.
 13. Zakir RM, Folefack A, Saric M, Berkowitz RL. The Use of Midodrine in Patients With Advanced Heart Failure. *Congest Heart Fail*. 2009;15(3):108–11.
 14. Sharma S, Bhambi B. Successful treatment of hypotension associated with stunned myocardium with oral midodrine therapy. *J Cardiovasc Pharmacol Ther*. 2005;10(1):77–9.
 15. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, *et al.* Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*. 1998;98(15):1510–6.
 16. Arena R, Guazzi M, Myers J, Peberdy MA. Prognostic value of heart rate recovery in patients with heart failure. *Am Heart J*. 2006;151(4):851.e7–13.
 17. Ponikowski P, Chua TP, Anker SD, Francis DP, Doehner W, Banasiak W, *et al.* Peripheral Chemoreceptor Hypersensitivity An Ominous Sign in Patients With Chronic Heart Failure. *Circulation*. 2001;104(5):544–9.
 18. Li M, Zheng C, Kawada T, Inagaki M, Uemura K, Sugimachi M. Adding the acetylcholinesterase inhibitor, donepezil, to losartan treatment markedly improves long-term survival in rats with chronic heart failure. *Eur J Heart Fail*. 2014;16(10):1056–65.
 19. Li M, Zheng C, Kawada T, Inagaki M, Uemura K, Shishido T, *et al.* Donepezil markedly improves long-term survival in rats with chronic heart failure after extensive myocardial infarction. *Circ J Off J Jpn Circ Soc*. 2013;77(10):2519–25.
 20. Lатарo RM, Silva CAA, Fazan R, Rossi MA, Prado CM, Godinho RO, *et al.* Increase in parasympathetic tone by pyridostigmine prevents ventricular dysfunction during the onset of heart failure *Am J Physiol Regul Integr Comp Physiol*. 2013;305(8):R908–16.
 21. Lara A, Damasceno DD, Pires R, Gros R, Gomes ER, Gavioli M, *et al.* Dysautonomia due to reduced cholinergic neurotransmission causes cardiac remodeling and heart failure. *Mol Cell Biol*. 2010;30(7):1746–56.
 22. Sabino JPJ, Silva CAA da, Giusti H, Glass ML, Salgado HC, Fazan R. Parasympathetic activation by pyridostigmine on chemoreflex sensitivity in heart-failure rats. *Auton Neurosci Basic Clin*. 2013;179(1):43–8.
 23. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol*. 2015;14(10):1023–36.
 24. Behling A, Moraes RS, Rohde LE, Ferlin EL, Nóbrega ACL, Ribeiro JP. Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmia and enhances heart rate variability in heart failure. *Am Heart J*. 2003;146(3):494–500.
 25. Serra SM, Costa RV, Teixeira De Castro RR, Xavier SS, Nóbrega ACLD. Cholinergic stimulation improves autonomic and hemodynamic profile during dynamic exercise in patients with heart failure. *J Card Fail*. 2009;15(2):124–9.
 26. Androne AS, Hryniewicz K, Goldsmith R, Arwady A, Katz SD. Acetylcholinesterase inhibition with pyridostigmine improves heart rate recovery after maximal exercise in patients with chronic heart failure. *Heart Br Card Soc*. 2003;89(8):854–8.

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