Review

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Use of midodrine in heart failure: a review

Sudarshan Gautam, MD[a], Saral Lamichhane, MBBS[d], Nava R. Sharma, MBBS[c,*], Prabal KC, MBBS[e], Arjun Basnet, MD[a], Sajog Kansakar, MD[c], Madalasa Pokhrel, MD[b], Vijay Shetty, MD[a], Norbert Moskovits, MD[a]

Abstract

Heart failure is a global health concern, affecting millions of individuals worldwide. Midodrine, an alpha-1 receptor agonist, might be a potential treatment option for patients with heart failure and concurrent hypotension. This review provides a comprehensive summary of the existing literature on the use of midodrine in heart failure patients, focusing on its pharmacology, epidemiology, and public health impact. Guideline-directed medical therapy (GDMT) is essential in heart failure management, but hypotension may limit its initiation or up-titration. Studies have shown that midodrine can improve blood pressure, reduce the need for vasopressor support, and enable the prescription of GDMT in patients who are intolerant to it due to hypotension. However, there are concerns over increased all-cause mortality in some studies, small sample sizes, and nonrandomized study designs in others. Further research, including large-scale randomized controlled trials and long-term follow-up studies, is needed to better understand the risks and benefits of midodrine use in heart failure patients, particularly in relation to GDMT. Clinicians should consider the potential advantages of midodrine against the limited evidence and potential risks before incorporating it into their clinical practice for heart failure treatment.

Keywords: cardiac failure, congestive cardiac failure, heart failure, hypotension, midodrine

Introduction

Heart failure (HF) is a complex condition characterized by impaired cardiac function and inadequate tissue perfusion, leading to many symptoms. It causes a significant increase in morbidity and mortality worldwide. HF was identified as an emerging epidemic of cardiovascular disease due to the steady rise in-hospital admissions, making it the most common cause of hospitalization among individuals aged 65 and older in 1997[1]. The global prevalence of HF is estimated at ~64.34 million, with 29 mild, 19 moderate, and 51% severe cases[2]. HF is responsible for 9.91 million years of life lost to disability, with an age-standardized prevalence rate highest in Central Europe, North Africa, and the Middle East and lowest in Eastern Europe and Southeast Asia[3]. The global economic burden of HF is estimated at $346.17 billion[3]. The estimated national cost of HF in 2012 was $30.7 billion, encompassing healthcare services, medications, and missed workdays. In the United States, about 6.2 million adults have HF[4]. As of 2018, it was among the leading causes of death in the country[5].

Guideline-directed medical therapy (GDMT) has been widely used to treat HF. But the progressive nature of HF, with its complex pathophysiology impacted by comorbidities, makes GDMT difficult to initiate and continue. Thus, more studies are required to know the complex pathophysiology of HF and the role of alternative drugs like Midodrine in its management.

HIGHLIGHTS

- Heart failure is a complex cardiac condition of global public health importance, affecting millions of individuals worldwide.
- Guideline-directed medical therapy has been widely used to treat heart failure.
- Midodrine might be a promising treatment option for patients with heart failure, particularly those with concurrent hypotension.

Methodology

A comprehensive search of relevant databases, including PubMed, Embase, and Google Scholar, was performed using a combination of keywords and MesH terms 'heart failure', 'cardiac failure', 'chronic heart failure', 'congestive cardiac failure', 'midodrine', 'hypotension', with the boolean operators. The search was limited to articles published in English from 1990 to the present; the final search was conducted on 3 March 2023. The articles were screened for relevance by title and abstract; duplicates were removed. The full texts of potentially relevant articles were reviewed, and the key findings were presented in the table.

[a]Maimonides Medical Center, Brooklyn, [b]Montefiore New Rochelle Hospital, New Rochelle, USA, [c]Manipal College of Medical Sciences, [d]Gandaki Medical College, Pokhara and [e]Kathmandu Medical College, Kathmandu, Nepal

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*Corresponding author. Address: Manipal College of Medical Sciences, Pokhara, 33700, Nepal. Tel.: +9779846718064. E-mail: navarajsharma19900227@gmail.com (N. R. Sharma).

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The relevant results were summarized in a narrative discussion along with the limitations and gaps in the current evidence.

Discussion

Heart failure

HF affects around 1–2% of the adult population. There are multiple factors that get stimulated after cardiac injuries and play vital roles in the development and progression of HF. Among the complex microstructural and cellular mechanisms, stretch-induced increase in the cardiac preload by the Frank-Starling mechanism, neurohormonal pathway activation, and macrovascular and microvascular changes in myocardial anatomy are thought to play important roles in HF[6].

There are mainly two types of HF. One is systolic HF, characterized by an impaired left ventricular contractility resulting in a reduced EF, also known as HF with reduced ejection fraction (HFrEF), and the other is diastolic HF with preserved ejection fraction (HFpEF). The various etiology of systolic HF are ischemic heart disease, cardiomyopathies, and valvular heart diseases[7]. The main structural change in HFrEF is eccentric hypertrophy or remodeling, followed by progressive volume overload and chamber dilatation, leading mainly to forward HF. In contrast, diastolic HF is mainly associated with chronic systemic hypertension or ischemic heart disease and is sometimes due to restrictive, infiltrative, or hypertrophic cardiomyopathies[8]. Diastolic HF is characterized by impaired ventricle filling and relaxation, which chronically leads to concentric remodeling or hypertrophy of the left ventricle thus, resulting in pressure overload and mainly backward HF. This HF differs in microscopic and structural pathophysiology and available treatment options.

Remodeling in heart failure

The term remodeling is used to infer the structural and subsequent functional changes in the heart after any cardiac injury. It includes changes in the heart's shape and mass[9,10]. Remodeling can be adaptive or physiological (like in an athlete's heart without fibrosis) and maladaptive or pathological[11]. Cardiac remodeling starts with myocyte hypertrophy, apoptosis, or proliferation. In addition, activating pro-inflammatory mediators leads to the induction of fibrosis[12]. These changes at the microscopic level produce cardiomyocyte reorganization and elongation leading to ventricular hypertrophy, increased wall tension, and subendocardial perfusion impairment.

Activation of the neurohumoral system

The pressure-baroreceptors at the carotid sinus, aortic arch, and the left ventricle are activated, activating the renin-angiotensin-aldosterone system, sympathetic nervous system, and release of vasoactive peptides. This leads to increased antidiuretic hormone arginine vasopressin release from the posterior pituitary gland. At the molecular level, this constant neurohumoral activation leads to transcriptional and post-transcriptional changes in the gene-regulating cardiac myocytes[13].

Activation of the immune system

The interplay between chronic inflammatory mediators plays a crucial role in HF patients' final pathogenesis of cardiac injury[14]. The mediators include TNFα, interleukin 1 (IL-1), and 6 (IL-6). Various studies are still going on about the use of this pro and anti-inflammatory mediator as a potential drug to halt the progression of HF[15].

Hypotension in advanced heart failure

Hypotension in advanced heart failure can occur for various reasons, as summarized in Table 1.

Treatment of heart failure

With the increasing life span in Western societies, the case of HFpEF is increasing, accounting for almost 50% of cases of HF[21]. Although the leading cause of HFpEF is left ventricular diastolic dysfunction, there are various contributory factors for HFpEF, like limited left ventricular systolic reserve, systemic and pulmonary vascular function, autonomic tone, etc[22]. Mainly because of this complex pathogenesis, there still exists a gap in the treatment of HFpEF, unlike with the treatment of HFrEF[23].

The treatment of HFrEF has greatly evolved over the past few decades with the use of Guideline-directed medical therapy (GDMT)[24]. Neurohormonal-blocking agents such as angiotensin-converting enzyme (ACE) inhibitors, certain beta-blockers (metoprolol succinate, carvedilol, and bisoprolol), angiotensin receptor blockers (ARBs), angiotensin receptor/neprilysin inhibitor (ARNI), sodium-glucose cotransporter 2 (SGLT2) inhibitors, and aldosterone antagonists have changed the mortality of HF. However, the progressive nature of HF, with its complex pathophysiology impacted by comorbidities makes treatment that can be effective at one stage of the disease become problematic as the disease progresses[25]. There are still a significant number of patients who develop low blood pressure during disease progression despite the use of GDMT. An increase in blood pressure, where the role of midodrine can be justified, may allow the tolerability of neurohormonal-blocking agents and improve outcomes in such patients.

Midodrine: drug pharmacology

Midodrine selectively stimulates alpha-1 receptors thereby increasing peripheral vascular resistance. It acts on peripheral venules and arterioles[26]. It is initially absorbed in a prodrug form and then metabolized by the liver into its active form[27]. As it does not exhibit beta-adrenergic activity, midodrine has no direct arrhythmogenic effects, unlike other intravenous vasopressors[28]. However, it should not be used in acute myocardial infarction as it may induce acute coronary vasospasm. Furthermore, midodrine's potential benefits in HF are being explored, particularly in preventing cardiac remodeling. This is thought to be achieved through direct agonism of alpha 1a adrenergic receptors, which are up-regulated due to high beta-adrenergic stimulation triggered by declining left ventricular ejection fraction[26]. Midodrine may address different causes of symptomatic hypotension, such as vasovagal syncope, orthostatic hypotension in geriatric patients, neuro-cardiogenic syncope, autonomic nervous system dysfunction, and hypotension induced by hemodialysis[27]. In advanced HF cases, there has been a recent trial in utilizing midodrine to increase blood pressure levels to the degree that enables the prescription of disease-modifying therapies[29]. However, this approach remains somewhat contentious.

Table 1

Causes of hypotension in advanced heart failure and their pathophysiology

Causes of hypotension in advanced heart failure	Pathophysiology
Advanced pump failure	Left ventricular pump failure in AHF results in a decreased ability of the heart to pump blood effectively, leading to reduced cardiac output and hypotension[16].
Neurohumoral dysfunction	Chronic neurohumoral activation (sympathetic and RAAS activation) induces Left Ventricular (LV) remodeling, which leads to the worsening of LV function leading to hypotension[17].
Medication side effects	Medications used to treat AHF, such as diuretics, vasodilators, and beta-blockers can cause hypotension as a side effect due to over-diuresis, dehydration, or vasodilation[18].
Cardiogenic shock	AHF can lead to cardiogenic shock due to pump failure, characterized by decreased cardiac output and severe hypotension[19].
Arrhythmias	Arrhythmias due to structural, electrophysiologic, metabolic, and hemodynamic changes in AHF can decrease cardiac output and exacerbate hypotension[20].

Midodrine in heart failure

The use of midodrine in HF has been the subject of several studies and investigations. The present review summarizes the current evidence regarding using of midodrine in HF, as outlined in Table 2).

In a study involving 60 patients, who were started on midodrine at the mean dose of 20.7 mg a day, 94% of the patients could tolerate Beta-Blockers (mostly carvedilol) or angiotensin receptor neprilysin inhibitors or mineralocorticoid receptor antagonists ($P<0.001$). The mean systolic blood pressure improvement was 8 (± 4) mmHg. Side effects like headache, palpitations, and jitteriness were found to be less than 5%. Although midodrine improved systolic blood pressure and was well-tolerated among patients, the small sample size and non-randomized study design limit its generalizability[30]. A retrospective study conducted at Mayo Clinic analyzed 1010 adult patients to identify the incidence of continuation of newly initiated midodrine upon ICU and hospital discharge and to identify associated risk factors. The study found that midodrine was continued in 67% of patients at ICU discharge and 34% at hospital discharge. Cardiovascular surgery ICU admission and mixed medical/surgical ICU admission were risk factors for midodrine continuation at ICU discharge. At the same time, congestive HF was a predictor of midodrine continuation at hospital discharge. Use of midodrine at ICU discharge was associated with a shorter ICU stay and a reduced risk of in-hospital mortality, but a higher risk of 1-year mortality at hospital discharge. However, further research is necessary to understand the long-term effects of its use and if the increased mortality is solely due to midodrine use[31].

A retrospective cohort study that analyzed the prevalence of midodrine prescription and its impact on all-cause mortality in 3640 hospitalized patients with decompensated HFrEF found 9.3% of patients were prescribed midodrine and 90.7% were not prescribed. All-cause mortality at 6 months was significantly higher in the midodrine group compared to those without midodrine
(26.4 vs. 3.9%). It also reported that patients prescribed midodrine were more likely to be prescribed beta-blockers, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin inhibitors. This study; however, has a possibility of selection bias in using midodrine in a sicker group of patients, and more research is needed to determine whether midodrine is an independent risk factor for mortality in patients with decompensated HF or a marker of a sicker population[32]. In a prospective study involving 10 patients with systolic HF and symptomatic hypotension interfering with optimizing medical therapy, the use of midodrine was associated with a higher percentage of patients on optimal HF therapy (ACE inhibitor/ARBs, beta-blockers, mineralocorticoid receptor antagonists) at the six-months follow-up[33]. With Midodrine therapy, systolic blood pressure increased from a baseline of 79.2 ± 4.6 to 99.0 ± 11 mmHg ($P<0.0004$), BNP decreased from 1402 ± 1559 to 706 ± 592 ($P<0.0001$), and NYHA Class decreased from 3.5 to 2.4 at 6 months. There was an improvement in left ventricular ejection fraction (baseline 24 ± 9.4 vs. 32.2 ± 9.9; $P<.001$), LVEDD decreased from a baseline of 6.2 cm to 5.9 cm ($P=0.04$), and a significant reduction in total hospital admissions (32 vs. 12; $P=0.02$) and total hospital days (150 vs. 58; $P=0.02$). Midodrine was well-tolerated with no reported side effects in patients. This study has the limitation of having a small size and lacks a control group, thus, further extensive studies are needed before making a favorable conclusion on midodrine use.

Another study highlighted the use of midodrine in a challenging situation in patients with severe congestive HF and low blood pressure requiring dialysis. Five patients with end-stage renal disease on outpatient dialysis and symptomatic HF with low blood pressure who received midodrine before and during their dialysis sessions showed an increase in the lowest mean arterial pressure during dialysis and in post-dialysis mean arterial pressure[34]. Symptoms of congestive HF were also found to have improved. In a case series involving four patients with hypotension secondary to left ventricular dysfunction, the use of midodrine in a nonfixed or dose titration manner served as bridge therapy for initiating or continuing GDMT with marked clinical improvement[35]. Improved blood pressure gains from midodrine initiation allowed marked improvement in systolic function with GDMT such as beta-blockers, angiotensin receptor neprilysin inhibitors, ACE inhibitor/ARBs, and/or spironolactone which reverse the cardiac remodeling. Even though these studies have shown the benefits of midodrine use, the results obtained from them cannot be generalized as they are conducted in a very small sample of patients.

Conclusion

Midodrine might be a promising treatment option for patients with HF, particularly those with concurrent hypotension. Current studies suggest that midodrine can improve blood pressure, reduce the need for vasopressor support, and improve

Table 2

Summary of the current evidence regarding using of midodrine in heart failure

Paper title	Journal	References	Number of participants	Findings
Midodrine As a Bridge to Enable Use of Life Enhancing Therapies in Chronic Heart Failure.	Journal of Cardiac Failure, 2020	Krishnaswami v., Desiree L., Teressa M. et. al[30]	60	After starting midodrine, 94% of the patients who were intolerant to BB, ACE/ARB and ANRI could tolerate BB (mostly carvedilol) or ARNI or MRA ($P < 0.001$). The mean improvement in SBP was 8 mm Hg, $\pm$ 4 mm Hg).
Continuation of Newly Initiated Midodrine Therapy After Intensive Care and Hospital Discharge: A Single-Center Retrospective Study	Critical Care Medicine, 2019	.Rizvi, Mahrukh S., Nei, Andrea M., Gajic, Ognjen, Mara, Kristin C., Barreto, Erin F[31]	1010	Discharge from the ICU on midodrine was associated with a significantly shorter ICU length of stay (7.5 ± 8.9 vs. 10.6 ± 13.4 days) and reduced risk of in-hospital mortality (hazard ratio, 0.47 [95% CI, 0.32-0.70]; $P < 0.001$), despite no difference in baseline severity of illness scores. In contrast, patients discharged from the hospital on midodrine had a higher risk of 1-year mortality (hazard ratio, 1.60 [95% CI, 1.26–2.04]; $P < 0.001$).
Prevalence of midodrine use in patients admitted with systolic congestive heart failure	Journal of American college of Cardiology, 2021	Christopher Scoma, Dae Hyun Lee, Adam Cohen, and Joel Fernandez[32]	3640	All-cause mortality at 6 months from hospitalization was significantly higher in the midodrine group compared to those without midodrine (26.4% vs. 3.9%; $P < 0.001$, RR 6.7, 95% CI 5.2%–8.5%).
The use of midodrine in patients with advanced heart failure.	Congestive Heart Failure, 2009	R. Zakir, A. Folefack, M. Saric, R. Berkowitz[33]	10	With Midodrine therapy, SBP increased from a baseline of 79.2 ± 4.6 to 99.0 ± 11 mmHg ($P < 0.0004$), BNP decreased from 1402 ± 1559 to 706 ± 592 ($P < 0.0001$), and NYHA Class decreased from 3.5 to 2.4 at 6 months. This led to an improvement in left ventricular ejection fraction (baseline 24 ± 9.4 vs. 32.2 ± 9.9; $P < 0.001$), LVEDD decreased from baseline of 6.2 cm to 5.9 cm ($P = 0.04$) and clinical outcomes, with a significant reduction in total hospital admissions (32 vs. 12; $P = 0.02$) and total hospital days (150 vs. 58; $P = 0.02$).
Hemodialysis in Hypotensive heart failure using midodrine	Am J Med Sci , 2009	Suzzane M. Bergman[34]	5	While receiving midodrine, each of the five patients on midodrine had less hypotension as measured by the MAP of the lowest blood pressures recorded during dialysis ($P < 0.03$).
Midodrine to optimize heart failure therapy in patients with concurrent hypotension	SAGE Open Medical Case Reports, 2022	Paul Shiu, G. S. Grewal, T. Kozik[35]	4	Exacerbations of heart failure with reduced ejection fraction may be ameliorated with outpatient midodrine titration among patients with baseline persistent hypotension.
Use of Midodrine in Heart Failure: Two Case Reports and a Review of the Literature	European Journal of Case Reports in Internal Medicine, 2022	Adnan Hajjiah, O. Maadarani, Z. Bitar, Boutros Hanna, R. Elshabasy, M. Abdelfatah, Mohammad Gohar[36]	2	Midodrine may be used off-label in patients with heart failure with reduced ejection fraction and symptomatic hypotension to allow optimization of medical therapy.

cardiac output. Improvement in blood pressure can provide a safe space to start goal-directed medical therapy for those intolerant to GDMT due to hypotension. However, conflicting findings of an increase in all-cause mortality in some studies are concerning. Thus, conducting more extensive studies and randomized controlled trials and investigating the long-term effects and risks associated with its use are necessary to provide evidence-based guidance for clinical practice. Clinicians should weigh the potential benefits of midodrine against the limited evidence and the potential risks before considering its use in HF.

Ethical approval

Not required.

Consent

Not applicable.

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Author contribution

S.G., N.R.S., S.L., P.K., A.B., and S.K. were involved in conceptualization, design and preparation of manuscript. V.S. and N.M. were involved in finalization of manuscript.

Declaration of competing interest

None.

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