

# Using MicroRNAs to Improve Neuromodulation Study Quantification

**Rochell Issa, Pratyush Pavan Devarasetty, Bindu Menon\***

Departments of Medical Education and Physiology & Pharmacology, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA

## Abstract

In recent years, neuromodulation has been gaining popularity as a potential therapy method for various ailments, including acute heart failure (AHF). There are currently five clinical trials using neuromodulation techniques to improve hemodynamics among patients with AHF. However, these studies can be limited by their outcome measurement methods as they utilize variables such as C-Reactive protein levels (CRP), or blood pressure (BP), and adverse events that can be easily confounded. Thus, we propose that micro-RNAs (miRNAs) have great potential to be reliable biomarkers that would significantly enhance outcome measurements of these studies as changing levels of various miRNAs are correlated with many different aspects of AHF.

**Keywords:** Neuromodulation; Micro-RNAs; Acute heart failure; Autonomic nervous system

\***Correspondence to:** Bindu Menon, Departments of Medical Education and Physiology & Pharmacology, University of Toledo College of Medicine and Life Sciences, 3105B CCEB, 2920 Transverse Dr., Toledo, OH 43614, USA; E-mail: [bindu.menon@utoledo.edu](mailto:bindu.menon@utoledo.edu)

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## Introduction

Neuromodulation refers to manipulating the autonomic nervous system using electrical, electromagnetic, and chemical methodologies for therapeutic use [1]. It strives for the long-term activation, inhibition, modification, and regulation of neural activity through alternating synaptic activity and potentiation [2]. It has been used for over 20 years in neurological diseases such as movement disorders like Parkinson's disease [3] and stroke [4].

More recently, there has been a growing interest in cardiovascular neuromodulation approaches due to the significant role that the autonomic nervous system plays in maintaining the integrity and proper functioning of the cardiovascular system (i.e., clinical studies using left ventricular assist devices (LVAD) and cardiac resynchronization therapy (CRT) for autonomic stimulation). Some of these approaches include vagus nerve stimulation [5], renal denervation [6], spinal cord stimulation [7], and baroreceptor activation therapy [8]. Heart failure has also been an increasingly popular topic of research within the field of neuromodulation as it remains the most common diagnosis for hospital admission in patients greater than 65 years of age [9]. Specifically, acute heart failure is associated with a 23% readmission rate at 30 days, a 6-fold increased mortality risk at 60 days, and a 2-fold increased mortality risk at two years [10].

Neuromodulation clinical studies focused on AHF have shown promise, although they conflict in the target site, duration of the study, and outcome measurement. Many of these studies are limited by their outcome measurement methods, ranging from easily

confounded protein markers like CRP and BP to measuring adverse events and mortality rates. Thus, there is a need for a more specific, reliable biomarker that can be tracked to assess the outcomes of these neuromodulation studies. Of recent, miRNAs have been gaining substantial traction as potential biomarkers for various disease states due to their ease of measurement, high specificity for tissue or cell types, durability, and practicality [11]. Given the growing interest and strength of data highlighting the benefit of using miRNAs as biomarkers in cardiovascular disease states, we are the first to suggest implementing miRNA measurements specifically into acute heart failure neuromodulation studies. This could be a promising strategy to obtain more efficient, robust, and specific outcome measurements in a rapidly growing cardiovascular device therapy research field.

## MiRNAs as Biomarkers in Acute Heart Failure

MiRNAs are non-coding sequences that play important roles in posttranscriptional gene regulation. They are required for nearly all cellular processes related to function and development. MiRNAs are remarkably resistant to several extreme conditions such as freeze-thaw cycles, boiling, and long-term storage, making them excellent candidates for use as biomarkers [12]. The recent discovery of their close involvement with the cardiovascular system makes their potential for biomarker use even more enticing. Although the current gold standard biomarkers for heart failure are highly sensitive B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), they are relatively non-specific [13]. In comparison, certain miRNAs have recently been discovered to be highly specific to stages and characteristics of heart failure [14]. This further supports



the potential for incorporating miRNAs in heart failure diagnosis and prognosis in response to therapy.

A thorough review by Vegter EL, et al. (2016) [15] provides strong support on the prognostic and diagnostic potential of miRNAs as biomarkers in heart failure, which we have summarized below. They cite that specific miRNAs are associated with left ventricular (LV) hypertrophy and fibrosis in hypertrophic cardiomyopathy, while other miRNAs are specific to different stages of acute heart failure, chronic heart failure, and heart failure with preserved ejection fraction (HFpEF) [15]. Interestingly, increases or decreases in serum levels of specific miRNAs have been associated with 180-day mortality and 2-year cardiovascular death rates post-hospitalization for acute heart failure [16]. For example, one recent study found that decreases in miR-18a-5p and miR-652-3p correlated to the 180-day mortality in hospitalization for acute heart failure [16]. MiRNAs such as miR-18a-5p, miR-126, miR-508-5p, and miR-652-3p have been found to correlate with high mortality rates post-hospitalization for acute heart failure. Other miRNAs have been associated with various other cardiovascular therapies as well. For example, studies comparing miR-1, miR-26b-5p, miR-30d, miR30e-5p, miR-208a/208b, miR-499, and miR-483-3p among controls and after successful left ventricular assist device therapy or cardiac resynchronization therapy reported increases or decreases in these miRNA levels at different time intervals post-hospitalization [17-19]. These reported trends of changing miRNA levels related to various cardiovascular disease states and therapies could be beneficially applied to improving outcomes measurements and prognostic values of ongoing clinical trials such as neuromodulation studies targeting AHF.

## Current Clinical Trials

There are five trials listed under the National Institutes of Health (NIH) U.S. National Library of Medicine that has either assessed or are currently assessing the improvement of hemodynamics in patients with AHF using neuromodulation. These trials can be found in the depository <https://clinicaltrials.gov>. These studies all use devices or transcutaneous methods to stimulate the cardiac autonomic and assess response in hospitalized AHF patients. They all assess hemodynamic variables during hospitalization for AHF and measure different outcome variables over varying lengths of time. For example, the OUHSC study measures changes in CRP, tumor necrosis (TNF) alpha, and interleukin (IL) levels during hospitalization for AHF during baseline and days 1-4, whereas Porto Alegre's study measures differences in blood levels of epinephrine, norepinephrine, and dopamine and improvement of heart rate variability one minute before and after transcutaneous electrical nerve stimulation intervention. Lastly, Cardionomic Inc measures the occurrence of all system and or procedure-related adverse events and serious adverse events and deaths associated with endovascular stimulation of the cardiac autonomic nerves in addition to standard of care (ClinicalTrials.gov).

## Conclusion

While these variables certainly help assess responses and track the potential improvement of AHF, they can be confounded by many other variables within the body. For example, although heart rate, blood pressure, cardiac output, Pulmonary capillary wedge pressure (PCWP), adverse events, and different cytokine levels strongly correlate with AHF, it is difficult to address the effect of confounding variables such as an underlying infection, stress, or other comorbidities play on these outcome measurements. Therefore, the use of specific

miRNA biomarkers for AHF and the response to HF neuromodulation treatments would significantly enhance the data of these clinical trials. The measurement of AHF-associated miRNAs would allow for the use of a reliable, specific, and minimally confounded variable that is easily quantifiable. Additionally, miRNA measurement would provide a more accurate and specific quantifiable comparison between controls and experimental groups to strengthen data further. The continuous measurement of these AHF-associated miRNAs would also allow for the quantification of the synaptic plasticity that neuromodulation studies strive for long-term in AHF patients to prevent rehospitalization. Thus, using miRNAs during hospitalization, post-treatment, and post-discharge would significantly enhance the outcome measurements of these studies and could ultimately help lead to better understanding and management of these patients.

## Summary

Due to the intricacy of the relationship between the cardiovascular system and the nervous system, neuromodulation studies focused on acute heart failure have been of increasing interest to researchers in the field of biotechnology devices. However, the invasive nature of these device therapies comes with several limitations, including the utilization of specific and non-confounding measurement variables. As miRNAs have recently been shown to be highly specific for AHF, their implementation as measurement variables in these studies shows vast promise and should be further explored.

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