Scholars LITERATURE

International Journal of Integrative Cardiology

Short Communication

DOI: https://doi.org/10.47275/2690-862X-126
Volume 4 Issue 1

Using MicroRNAs to Improve Neuromodulation Study Quantification

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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

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Citation: Issa R, Devarasetty PP, Menon B (2022) Using MicroRNAs to Improve Neuromodulation Study Quantification. Int J Integr Cardiol, Volume 4:1. 126. DOI: https://doi.org/10.47275/2690-862X-126

Received: July 01, 2021; **Accepted:** July 22, 2021; **Published:** July 29, 2021

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 Trails

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 autonomics 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.

References

1. Krames ES, Peckham PH, Rezai AR, Aboelsaad F (2009) What is Neuromodulation? In: Krames ES, Peckham PH, Rezai AR, (Eds). 1st (editn) Neuromodulation. San Diego: Academic Press. 3-8.
2. Johnson MD, Lim HH, Netoff TI, Connolly AT, Johnson N, et al. (2013) Neuromodulation for brain disorders: challenges and opportunities. IEEE Trans Biomed Eng 60: 610-624. https://doi.org/10.1109/TBME.2013.2244890
3. Brittain JS, Cagnan H (2018) Recent trends in the use of electrical neuromodulation in parkinson's disease. Curr Behav Neurosci Rep 5: 170-178. https://doi.org/10.1007/s40473-018-0154-9
4. Caglayan AB, Beker MC, Caglayan B, Yalcin E, Caglayan A, et al. (2019) Acute and Post-acute Neuromodulation Induces Stroke Recovery by Promoting Survival Signaling, Neurogenesis, and Pyramidal Tract Plasticity. Front Cell Neurosci 13: 144. https://doi.org/10.3389/fncel.2019.00144
5. Stavrakis S, Humphrey MB, Scherlag B, Iftikhar O, Parwani P, et al. (2017) Low-level vagus nerve stimulation suppresses post-operative atrial fibrillation and inflammation: a randomized study. J Am Coll Cardiol EP 3: 929-938. https://doi.org/10.1016/j.jacep.2017.02.019
6. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, et al. (2012) A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol 60: 1163-1170. https://doi.org/10.1016/j.jacc.2012.05.036
7. Tse HF, Turner S, Sanders P, Okuyama Y, Fujiu K, et al. (2015) Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS HEART study): first-in-man experience. Heart Rhythm 12: 588-595. https://doi.org/10.1016/j.hrthm.2014.12.014
8. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, et al. (2015) Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. J Am Coll Cardiol HF 3: 487-496. https://doi.org/10.1016/j.jchf.2015.02.006
9. Albert C, Estep JD (2019) Economic impact of chronic heart failure management in today's cost-conscious environment. Card Electrophysiol Clin 11: 1-9. https://doi.org/10.1016/j.ccep.2018.11.002
10. Orso F, Fabbri G, Maggioni AP (2017) Epidemiology of heart failure. Handb Exp Pharmacol 243: 15-33. https://doi.org/10.1007/164_2016_74
11. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, et al. (2020) miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis. Cells 9: 276. https://doi.org/10.3390/cells9020276

12. Chen X, Ba Y, Ma L, Cai X, Yin Y, et al. (2008) Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res 18: 997-1006. https://doi.org/10.1038/cr.2008.282

13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, et. Al. (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur Heart J 33: 1787-1847. https://doi.org/10.1093/eurheartj/ehs104

14. Chen F, Yang J, Li Y, Wang H (2018) Circulating microRNAs as novel biomarkers for heart failure. Hellenic J Cardiol 59: 209-214. https://doi.org/10.1016/j.hjc.2017.10.002

15. Vegter EL, van der Meer P, de Windt LJ, Pinto YM, Voors AA (2016) MicroRNAs in heart failure: from biomarker to target for therapy. Eur J Heart Fail 18: 457-468. https://doi.org/10.1002/ejhf.495

16. Ovchinnikova ES, Schmitter D, Vegter EL, Ter Maaten JM, Valente MA, et al. (2015) Signature of circulating microRNAs in patients with acute heart failure. Eur J Heart Fail 18: 414-423. https://doi.org/10.1002/ejhf.332

17. Marfella R, Di Filippo C, Potenza N, Sardu C, Rizzo MR, et al. (2013) Circulating microRNA changes in heart failure patients treated with cardiac resynchronization therapy: responders vs. non-responders. Eur J Heart Fail 15: 1277-1288. https://doi.org/10.1093/eurjhf/hft088

18. Melman YF, Shah R, Danielson K, Xiao J, Simonson B, et al. (2015) Circulating MicroRNA-30d is associated with response to cardiac resynchronization therapy in heart failure and regulates cardiomyocyte apoptosis: a translational pilot study. Circulation 131: 2202-2216. https://doi.org/10.1161/CIRCULATIONAHA.114.013220

19. Morley-Smith AC, Mills A, Jacobs S, Meyns B, Rega F, et al. (2014) Circulating microRNAs for predicting and monitoring response to mechanical circulatory support from a left ventricular assist device. Eur J Heart Fail 16: 871-879. https://doi.org/10.1002/ejhf.116