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[BISC9-01(Invited)] Toward non-invasive, precise control of internal organs via ultrasound neuromodulation of the autonomic nervous system

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Neuromodulation is a technology for reversibly modulating neural activity by applying artificial stimuli to an organism, and ultrasound neuromodulation is promising with its superior spatial and time resolution. Here we briefly mention the current situation of ultrasound neuromodulation and the neuromodulation of the autonomic nervous system.

Toward non-invasive, precise control of internal organs via ultrasound neuromodulation of the autonomic nervous system

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ABSTRACT

Neuromodulation is a technology for reversibly modulating neural activity by applying artificial stimuli to an organism. Electrical and magnetic stimulation technologies have been employed in clinical practices, especially for brain disorders including motor and mood disorders. Ultrasound stimulation has theoretically superior spatial and time resolution to electrical and magnetic stimulation. Even cell-type specific non-invasive neuromodulation is possible with an emerging technology with mechano-sensitive ion channels. Here we briefly mention the current situation of ultrasound neuromodulation and the neuromodulation of the autonomic nervous system. An application of the ultrasound neuromodulation of an organ controlled by the autonomic nervous system (such as the cardiovascular system) is then discussed.

Keywords: Neuromodulation, Non-invasive brain stimulation, Ultrasound, Sonogenetics, Autonomic Nervous System, Cardiovascular system

1. INTRODUCTION

Neuromodulation is a technique for reversibly modulating neural activity by applying artificial stimuli to an organism via devices or other means. Neuromodulation has made it possible to control drug-resistant cases of brain disorders such as epilepsy, Parkinson's disease, depression, etc.[1] The most commonly used modality of neuromodulation has been electrical stimulation, which is used clinically as deep brain stimulation or transcranial electrical stimulation. Magnetic stimulation is also used as transcranial stimulation, especially for modulating symptoms of psychiatric disorders like major depressive disorder. However, these modalities have shortcomings such as the invasiveness associated with electrode insertion, low spatial resolution, and lack of cell-type specificity. Ultrasound is a relatively new modality for neuromodulation that complements the shortcomings of electric and magnetic neuromodulation. It has excellent bio-permeability and can be delivered from outside the body (non-invasiveness), stimulus focus can be achieved by focusing its irradiation from multiple transducers (high spatial resolution), and it has the ability to temporally follow various stimulation patterns in sub-milliseconds (good temporal resolution). Thus, ultrasound makes it possible to non-invasively and highly precisely stimulate neuronal nuclei in deep brain structures. Ultrasound neuromodulation can be utilized not only to control disorders of the central nervous system (CNS), but also to control those of the autonomic nervous system (ANS). Thus, here we briefly review our knowledge of ultrasound neuromodulation and neuromodulation of the ANS. We then discuss possible applications of ultrasound neuromodulation of the ANS for controlling internal organs, mainly the heart.

2. ULTRASOUND NEUROMODULATION

Ultrasound can be utilized to modulate neuronal activities in either direct or indirect ways. Firstly, ultrasound can directly excite or inhibit neuronal activities via modulating mechanosensitive ion channels or lipid bilayers.[2] It can open mechanosensitive ion channels by applying mechanical forces to cell membranes and the cytoskeleton.[3,4] Ultrasound irradiation can modulate the intact brain via endogenous mechanosensitive ion channels such as Piezo channels and transient receptor potential channels.[5,6] The overexpression of exogenous or endogenous ultrasound-sensitive channels or other molecules in a defined cell population can enhance the responses of neural activities to ultrasound (sonogenetics).[7] Ultrasound may cause small pores of the plasma membrane and it may result in depolarization. Much research and development has been conducted to utilize ultrasound neuromodulation technologies for controlling brain disorders such as epilepsy.[8]

Ultrasound is also utilized to indirectly modulate neural activities such as brain region-specific drug or gene delivery, which is mediated by the transient opening of the blood-brain barrier (BBB) with lipid-based microbubbles. Transracial-focused ultrasound stimulation causes contraction and expansion of intravenously administered, ultrasound-sensitive microbubbles in the brain capillaries, which pushes tight junctions between vascular endothelial cells and transiently opens the BBB. Currently, this ultrasound-mediated, targeted-drug delivery is under investigation for therapies of Alzheimer's disease,[9] Parkinson's disease,[10] amyotrophic lateral sclerosis,[11] and brain tumors.[12, 13] Ultrasound-mediated BBB opening also enables non-invasive, targeted-gene delivery in small and large brain regions.[14, 15]

3. NEUROMODULATION OF AUTONOMIC NERVOUS SYSTEM

The ANS maintains the homeostasis of systemic organs and tissue with an extensive network via multiple level reflex controls. The sympathetic nerve and parasympathetic nerve compose normal autonomic tone with opposite functions and complementary ganglia positions. Hence, the selective bilateral modulation of the ANS would redress dysfunctions of the regulatory circuits and treat disease progression. To date, neuromodulation technologies have allowed attempts to modulate specific neural circuits to control targeted organs. Vagus nerve stimulation has been revealed as an effective way for treating inflammation diseases and heart failure.[16-18] Baroreflex activation therapy was also tested to relieve refractory hypertension.[19-22] In abdominal targets, vagal nerve blockade has been demonstrated as a therapeutic method to alleviate obesity.[23-26] For lower urinary and digestive tract innervation, sacral nerve stimulation has been used to treat pelvic dysfunctions such as incontinence.[27-29] For chronic stimulation therapy, proper devices with closed-loop control would improve patient compliance and effects.[1, 30, 31] These neuromodulation technologies may be replaced by those with ultrasound for enhanced safety and effectiveness.

4. NEUROMODULATION OF CARDIOVASCULAR DISEASES

Sympathetic hyperactivity and parasympathetic hypoactivity underlie many cardiovascular diseases such as hypertension, acute myocardial infarction and heart failure.[32-34] Therefore, the imbalance of the ANS can be a therapeutic target. In baroreflex activation therapy, the baroreceptors of the carotid sinus nerve would be electrically activated, then sympathetic activity and heart rate would be inhibited via the reflex arc, resulting in a decrease of blood pressure. In recent years, neuromodulation devices have shown effectiveness and safety in clinical trials for refractory hypertension.[22, 35-37] Deep brain stimulation of the midbrain periaqueductal grey has been tested to effectively influence blood pressure and heart rate variability,[38-40] which provides a possible therapeutic target. The spinal cord has utility in reducing sympathetic activity with largely major autonomic ganglia. Spinal cord stimulation in T1-T3 levels has been shown to be a safe and feasible treatment for heart failure[41] (but see Zipes *et al*., 2016).[42] Bilateral stellate ganglia innervate the left ventricle and are remodeled with hypertrophy, inflammation and oxidative stress in cardiomyopathy and ventricular arrhythmia patients. Therefore, bilateral stellectomy (known as cardiac sympathetic denervation) has demonstrated efficacy in heart failure and refractory ventricular arrhythmia as an intrinsic cardiac neuromodulation.[43, 44] Additionally, renal denervation can decrease abnormal sympathetic afferent activity caused by noradrenaline spillover. Bilateral renal denervation has been a reported result of reduced arrhythmic burden in several clinical trials.[45-47] Cervical vagus nerve stimulation has substantially elevated the parasympathetic activity and restored autonomic tone balance. However, clinical trials have failed to demonstrate the improvement of heart failure symptoms.[48, 49] On the other hand, another ANTHEM-HF study showed improvements in cardiac function and heart failure symptoms.[50-52] Different stimulation parameters and devices were used in these trials which might explain the variety of efficacy. The tragus is innervated by the auricular branch of the vagus nerve and this branch enables transcutaneous vagus nerve stimulation from the tragus in humans.[53] The parasympathetic activity was significantly decreased by the tragus stimulation.[54] Low-level tragus stimulation has suppressed atrial fibrillation and decreased inflammatory cytokines in patients.[55] In patients with diastolic dysfunction, left ventricle longitudinal mechanics acutely improved under right tragus stimulation.[18] Transcranial-focused ultrasound stimulation targeting the baroreflex circuits, the medulla cardiovascular autonomic centers, and the vagus nerve itself or its motor nucleus may be a safe and effective therapeutic strategy.

5. CONCLUSION

Here our current knowledge of ultrasound neuromodulation technologies and neuromodulation therapies for ANS disorders is provided. The ability to non-invasively stimulate neural nuclei deep in the brain is particularly important because it complements the shortcomings of electrical and magnetic stimulation. The implementation of wearable ultrasound neuromodulation devices combined with the real-time processing of biological signals is also expected to lead to on-demand neural activity intervention methods. These technologies can be combined to implement real-time control of the cardiac functions via time and organ-specific, transcranial-focused ultrasound stimulation of the medulla cardiovascular autonomic centers. These topics will be discussed further at the conference.

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REFERENCES

[1] Takeuchi, Y., and Berényi, A., “Oscillotherapeutics – Time-targeted interventions in epilepsy and beyond”, Neurosci. Res. 152, 87-107 (2020).
[2] Yu, K., Niu, X., Krook-Magnuson, E., *et al.*, “Intrinsic functional neuron-type selectivity of transcranial focused ultrasound neuromodulation.,” Nat. Commun. 12, 2519 (2021).
[3] Kubanek, J., Shukla, P., Das, A., *et al.*, “Ultrasound elicits behavioral responses through mechanical effects on neurons and ion channels in a simple nervous system,” J. Neurosci. 38 (12), 3081-3091 (2018).
[4] Yoo, S., Mittelstein, D. R., Hurt, R. C., *et al.*, “Focused ultrasound excites cortical neurons via mechanosensitive calcium accumulation and ion channel amplification,” Nat Commun 13, 493 (2022).
[5] Qiu, Z., Guo, J., Kala, S., Zhu, J., *et al.*, “The mechanosensitive ion channel Piezo1 significantly mediates in vitro ultrasonic stimulation of neurons,” iScience 21, 448-457 (2019).
[6] Ranade, S. S., Syeda, R., and Patapoutian, A., Mechanically Activated Ion Channels,” Neuron 87 (6), 1162-1179 (2015).
[7] Wang, S., Meng, W., Ren, Z., *et al.*, “Ultrasonic neuromodulation and sonogenetics: A new era for neural modulation,” Front. Physiol. 11, 787 (2020).
[8] Li, X., Yang, H., Yan, J., *et al.*, “Seizure control by low-intensity ultrasound in mice with temporal lobe epilepsy,” Epilepsy Res. 154, 1-7 (2019)
[9] Liu, X., Sta Maria, N. S., Lin S. W., *et al.*, “The applications of focused ultrasound (FUS) in Alzheimer's disease treatment: A systematic review on both animal and human studies,” Aging Dis. 12(8), 1977-2002 (2021).
[10] Gasca-Salas, C., Fernández-Rodríguez, B., Pineda-Pardo, J. A., *et al.*, “Blood-brain barrier opening with focused ultrasound in Parkinson’s disease dementia,” Nat. Commun. 12, 779 (2021).
[11] Abrahao, A., Meng, Y., Llinas, M., *et al.* “First-in-human trial of blood–brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound,” Nat. Commun. 10, 4373 (2019).
[12] Mainprize, T., Lipsman, N., Huang, Y., *et al.* “Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: A clinical safety and feasibility study,” Sci. Rep. 9, 321 (2019).
[13] Sun, T., Zhang, Y., Power, C., *et al.*, “Closed-loop control of targeted ultrasound drug delivery across the blood-brain/tumor barriers in a rat glioma model,” Proc. Natl. Acad. Sci. U. S. A. 114 (48), E10281-E10290 (2017).
[14] Ogawa, K., Kato N., Yoshida M., *et al.*, “Focused ultrasound/microbubbles-assisted BBB opening enhances LNP-mediated mRNA delivery to brain,” J. Control. Release 348, 34-41 (2022).
[15] Nouraein, S., Lee, S., Saenz, V. A., *et al.*, “Acoustically targeted noninvasive gene therapy in large brain regions,” bioRxiv 2023.01.19.52626 (2023).
[16] Bonaz, B., Sinniger, V., Hoffmann,D., *et al.*, “Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study,” Neurogastroenterol. Motil. 28(6), 948-953 (2016).
[17] Koopman, F. A., Chavan, S. S., Miljko, S., *et al.*, “Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis,” Proc. Natl. Acad. Sci. U. S. A. 113(29), 8284-8289 (2016).
[18] Tran, N., Asad, Z., Elkholey K., *et al.*, “Autonomic neuromodulation acutely ameliorates left ventricular strain in humans,” J. Cardiovasc. Transl. Res. 12(3), 221-230 (2019).
[19] Wallbach, M., Born, E., Kampfer, D., *et al.*, “Long-term effects of baroreflex activation therapy: 2-year follow-

up data of the BAT Neo system," Clin. Res. Cardiol. 109(4), 513-522 (2020).
[20] Gordin, D., Fadl Elmula, F. E. M., Andersson, B., *et al.*, "The effects of baroreflex activation therapy on blood pressure and sympathetic function in patients with refractory hypertension: the rationale and design of the Nordic BAT study," Blood Press., 26(5), 294-302 (2017).
[21] Beige, J., Jentzsch, T., Wendt, R., *et al.*, "Blood pressure after blinded, randomized withdrawal, and resumption of baroreceptor-activating therapy," J. Hypertens. 35(7), 1496-1501 (2017).
[22] Bisognano, J. D., Bakris, G., Nadim, M. K., *et al.*, "Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial," J. Am. Coll. Cardiol. 58(7), 765-773 (2011).
[23] Camilleri, M., Toouli, J., Herrera, M. F., *et al.*, "Intra-abdominal vagal blocking (VBLOC therapy): clinical results with a new implantable medical device," Surgery 143(6), 723-731 (2008).
[24] Ikramuddin, S., Blackstone, R. P., Brancatisano, A., *et al.*, "Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: the ReCharge randomized clinical trial," JAMA 312(9), 915-922 (2014).
[25] Apovian, C. M., Shah, S. N., Wolfe, B. M., *et al.*, "Two-year outcomes of vagal nerve blocking (vBloc) for the treatment of obesity in the ReCharge Trial," Obes. Surg. 27(1), 169-176 (2017).
[26] Sarr, M. G., Billington, C. J., Brancatisano, R., *et al.*, "The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity," Obes. Surg. 22(11), 1771-1782 (2012).
[27] Dmochowski, R. R. and Gomelsky, A., "Update on the treatment of overactive bladder," Curr. Opin. Urol. 21(4), 286-290 (2011).
[28] Drake, M. J., Apostolidis, A., Cocci, A., *et al.*, "Neurogenic lower urinary tract dysfunction: Clinical management recommendations of the neurologic incontinence committee of the fifth international consultation on incontinence 2013," Neurourol. Urodyn. 35(6), 657-665 (2016).
[29] Siegel, S. W., Catanzaro, F., Dijkema, H. E., *et al.*, "Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention," Urology, 56(6 Suppl 1), 87-91 (2000).
[30] Cracchiolo, M., Ottaviani, M. M., Panarese, A., *et al.*, "Bioelectronic medicine for the autonomic nervous system: clinical applications and perspectives," J. Neural. Eng. 18, 041002 (2021).
[31] Yap, J. Y. Y., Keatch, C., Lambert, E., *et al.*, "Critical review of transcutaneous vagus nerve stimulation: challenges for translation to clinical practice," Front. Neurosci. 14, 284 (2020).
[32] Krum, H., Schlaich, M., Whitbourn, R., *et al.*, "Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study," Lancet 373(9671), 1275-1281 (2009).
[33] Cohn, J. N., Levine, T. B., Olivari, M. T., *et al.*, "Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure," N. Engl. J. Med. 311(13), 819-823 (1984).
[34] La Rovere, M. T., Bigger Jr., J. T., Marcus, F. I., *et al.*, "Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators," Lancet 351(9101), 478-484 (1998).
[35] de Leeuw, P. W., Bisognano, J. D., Bakris, G. L., *et al.*, "Sustained reduction of blood pressure with baroreceptor activation therapy: Results of the 6-year open follow-up," Hypertension 69(5), 836-843 (2017).
[36] Wilks, S. J., Hara, S. A., Ross, E. K., *et al.*, "Non-clinical and pre-clinical testing to demonstrate safety of the Barostim neo electrode for activation of carotid baroreceptors in chronic human implants," Front. Neurosci. 11, 438 (2017).
[37] Weaver, F. A., Abraham, W. T., Little, W. C., *et al.*, "Surgical experience and long-term results of baroreflex activation therapy for heart failure with reduced ejection fraction," Semin. Thorac. Cardiovasc. Surg. 28(2), 320-328 (2016).
[38] Sverrisdottir, Y. B., Green, A. L., Aziz, T. Z., *et al.*, "Differentiated baroreflex modulation of sympathetic nerve activity during deep brain stimulation in humans," Hypertension 63(5), 1000-1010 (2014).
[39] Pereira, E. A., Lu, G., Wang, S., *et al.*, "Ventral periaqueductal grey stimulation alters heart rate variability in humans with chronic pain," Exp. Neurol. 223(2), 574-581 (2010).
[40] Green, A. L., Wang, S., Owen, S. L., *et al.*, "Deep brain stimulation can regulate arterial blood pressure in awake humans," Neuroreport 16(16), 1741-1745 (2005).
[41] Tse, H. F., Turner, S., Sanders, P., *et al.*, "Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS HEART study): first-in-man experience," Heart Rhythm, 12(3), 588-595 (2015).

[42] Zipes, D. P., Neuzil, P., Theres, H., *et al.*, "Determining the feasibility of spinal cord neuromodulation for the treatment of chronic systolic heart failure: The DEFEAT-HF Study," JACC Heart Fail. 4(2), 129-136 (2016).
[43] Vaseghi, M., Gima, J., Kanaan, C., *et al.*, "Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up," Heart Rhythm 11(3), 360-366 (2014).
[44] Vaseghi, M., Barwad, P., Malavassi Corrales, F. J., *et al.*, "Cardiac sympathetic denervation for refractory ventricular arrhythmias," J. Am. Coll. Cardiol. 69(25), 3070-3080 (2017).
[45] Armaganijan, L. V., Staico, R., Moreira, D. A., *et al.*, "6-Month outcomes in patients with implantable cardioverter-defibrillators undergoing renal sympathetic denervation for the treatment of refractory ventricular arrhythmias," JACC Cardiovasc. Interv. 8(7), 984-990 (2015).
[46] Ukena, C., Mahfoud, F., Ewen, S., *et al.*, "Renal denervation for treatment of ventricular arrhythmias: data from an international multicenter registry," Clin. Res. Cardiol. 105(10), 873-879 (2016).
[47] Remo, B. F., Preminger, M., Bradfield, J., *et al.*, "Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy," Heart Rhythm, 11(4), 541-546 (2014).
[48] Gold, M. R., Van Veldhuisen, D. J., Hauptman, P. J., *et al.*, "Vagus nerve stimulation for the treatment of heart failure: The INOVATE-HF Trial," J. Am. Coll. Cardiol. 68(2), 149-158 (2016).
[49] Zannad, F., De Ferrari, G. M., Tuinenburg, A. E., *et al.*, "Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial," Eur. Heart J. 36(7), 425-433 (2015).
[50] Premchand, R. K., Sharma, K., Mittal, S., *et al.*, "Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial," J. Card. Fail. 20(11), 808-816 (2014).
[51] DiCarlo, L. A., Libbus, I., Kumar, H. U., *et al.*, "Autonomic regulation therapy to enhance myocardial function in heart failure patients: the ANTHEM-HFpEF study," ESC Heart Fail. 5(1), 95-100 (2018).
[52] Nearing, B. D., Libbus, I., Amurthur, B., *et al.*, "Acute autonomic engagement assessed by heart rate dynamics during vagus nerve stimulation in patients with heart failure in the ANTHEM-HF trial," J. Cardiovasc. Electrophysiol. 27(9), 1072-1077 (2016).
[53] Fallgatter, A. J., Neuhauser, B., Herrmann, M. J., *et al.*, "Far field potentials from the brain stem after transcutaneous vagus nerve stimulation," J. Neural. Transm. (Vienna) 110(12), 1437-1443 (2003).
[54] Clancy, J. A., Mary, D. A., Witte, K. K., *et al.*, "Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity," Brain Stimul. 7(6), 871-877 (2014).
[55] Stavrakis, S., Humphrey, M. B., Scherlag, B. J., *et al.*, "Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation," J. Am. Coll. Cardiol. 65(9), 867-875 (2015).