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Data Descriptor

The Effect of Short-Term Transcutaneous Electrical Stimulation of Auricular Vagus Nerve on Parameters of Heart Rate Variability

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Abstract: Many previous studies have demonstrated that transcutaneous vagus nerve stimulation (VNS) has the potential to exhibit therapeutic effects similar to its invasive counterpart. An objective assessment of VNS requires a reliable biomarker of successful vagal activation. Although many potential biomarkers have been proposed, most studies have focused on heart rate variability (HRV). Despite the physiological rationale for HRV as a biomarker for assessing vagal stimulation, data on its effects on HRV are equivocal. To further advance this field, future studies investigating VNS should contain adequate methodological specifics that make it possible to compare the results between studies, to replicate studies, and to enhance the safety of study participants. This article describes the design and methodology of a randomized study evaluating the effect of short-term noninvasive stimulation of the auricular branch of the vagus nerve on parameters of HRV. Primary records of rhythmograms of all the subjects, as well as a dataset with clinical, instrumental, and laboratory data of all the current study subjects are in the public domain for possible secondary analysis to all interested researchers. The physiological interpretation of the obtained data is not considered in the article.

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Keywords: auricular stimulation; auricular vagus nerve stimulation; transcutaneous auricular vagus nerve stimulation; heart rate variability; parasympathetic nervous system

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1. Summary

Current knowledge of the vagus nerve anatomy in conjunction with evidence from basic experimental and clinical research has contributed to the fact that vagus nerve stimulation (VNS) is now actively investigated as a potential therapy for a number of conditions, including epilepsy [1–3], depression [4,5], migraine [6], tinnitus [7], heart failure [8–10], and other diseases [11–14]. There are two main methods of VNS: invasive and noninvasive (transcutaneous). Invasive VNS is used as a neuromodulatory technique for the treatment of depression and epilepsy in severe clinical cases where medicinal therapy has no significant effect on the disease. The method was approved by the U.S. Food and Drug

Administration (FDA) in 1997 [15]. The implantable device (neurostimulator) consists of an electrode wrapped around the left vagus nerve and an implantable unit with a battery and a programmable pulse generator located under the collarbone. Although minimally invasive, the procedure is associated with various complications. The most common of them are bradyarrhythmia, the development of peritracheal hematoma, local infection (around the wound), dysfunction of the vocal cords and a subsequent change of the voice, shortness of breath, neck pain, cough, difficulty swallowing, etc. [16,17]. In addition, during the implantation of the neurostimulator, the vagus nerve is separated from the carotid artery in order to place the electrodes, which is also associated with an increased risk of arterial injury.

Transcutaneous VNS is a new alternative technique that is noninvasive, safe, and inexpensive. The main goal of developing this method was to overcome the limitations that exist for invasive stimulation, as well as to evaluate the physiological effects of such stimulation. A number of studies have shown that transcutaneous VNS has the potential to exhibit the therapeutic effects similar to those of its invasive counterpart. The stimulation is performed in specific locations by surface electrodes using low-frequency electrical currents, habitually aimed at the auricular branch of the vagus nerve (ABVN) or its cervical branch [18–20]. There are two possible explanations regarding the physiological mechanisms of noninvasive transcutaneous stimulation. The first of these implies that the stimulation of ABVN is associated with the activation of the afferent fibers of the vagus (ear → brain → vagus nerve → organ). The second mechanism implied involves direct activation of the efferent projections of the vagus nerve from the ear to the organs of the body (ear → vagus nerve → heart) [21]. Various diseases can lead to the loss or disruption of afferent feedback with the brain, making it impossible for the brain to adapt to changes in organs, functions, and/or environmental factors. As a physiological hypothesis, it is assumed that stimulation of the vagus fibers replaces the lost or impaired afferent feedback with the brain, causing systemic regeneration processes that can lead to a steady restoration of the functions of controlled organs, along with the repair of the corresponding sensory feedback [19].

ABVN stimulation activates vagal sensory fibers, thereby mimicking the sensory input to the brainstem and forming the so-called auriculo–vagal afferent pathway [22]. These fibers are projected directly onto the nucleus of the solitary tract (NST), which, in turn, has direct or indirect projections onto the nuclei that provide noradrenergic, endorphinergic, and serotonergic fibers in various parts of the brain that regulate the systemic parameters of the cardiovascular, respiratory, and immune functions. Hence, the expected body's response to ABVN stimulation is systemic.

In most studies, the left vagus nerve has been the preferred site of stimulation. The study performed on animals by Ardell J.L. et al. established that the stimulation of the right vagus nerve was associated with an increased incidence of bradycardia, while left-sided stimulation was relatively safe [23]. This was associated with the fact that the right vagus predominantly innervates the sinoatrial node (SA), whereas the left vagus mostly innervates the atrioventricular (AV) node. It is also worth noting that the location around which the electrodes are wrapped during an invasive implantation of a VNS device in humans does not include its upper or lower branches going to the heart [24]. Despite this, the FDA-approved labeling of the VNS Therapy System devices implies that it is only intended for stimulating the left vagus nerve in the neck within the carotid sheath.

Currently, the use of transcutaneous stimulation of the ABVN is not limited to the treatment of depression and epilepsy. Its effect on the body has been studied in numerous publications, as well as in other disorders. Particular attention is paid to studying the efficacy of ABVN stimulation in various cardiovascular diseases (CVD) [25]. One of the key features mediating various CVDs (such as heart failure, hypertension, and obstructive sleep apnea) is sympathetic tone. This is due to the presence of a generally recognized connection between sympathetic activity and the production of biologically active molecules, high and stable levels of which adversely affect the heart and circulatory system. Consequently, the

issue of using ABVN stimulation in heart failure as a means of modulating sympathovagal imbalance is currently actively being investigated. The obtained results showed that chronic VNS improved left ventricular function and patient survival [8–10].

The lack of similarity between behavioral studies, as well as numerous theories of physiological processes during VNS, make it necessary to determine a reliable biomarker for successful vagus nerve activation. Although many potential biomarkers have been proposed, most studies have focused on heart rate variability (HRV).

Despite the physiological rationale for HRV as a biomarker for evaluating ABVN stimulation, data on its effects on HRV are equivocal. Some studies established a significant decrease in the ratio of spectral characteristics LF/HF (low-frequency/high-frequency oscillations) during active stimulation compared with sham stimulation, implying an increase in the parasympathetic component of HRV [26–29]. However, other studies found no increase in HRV [30–34]. In addition, the issue of large methodological differences between studies remains important (e.g., different stimulation devices, stimulation sides (left vs. right) and precise locations, experimental design, reported HRV parameters, and stimulation protocols). All these factors reduce the comparability of the studies.

To further advance this field, future studies investigating VNS should contain adequate methodological details making it possible to compare the results between studies, to replicate studies, and to improve the safety of study participants. Accordingly, in 2021, the first international consensus document and recommendations for minimum reporting standards in studies on transcutaneous VNS were published [35]. Authors from 88 institutions around the world proposed a minimum set of reported indicators to manage future research in this area. The proposed items are related to the specific technical aspects of the device and stimulation parameters, as well as general recommendations, inclusion and exclusion criteria for participants, description of the results, and side effects.

Hence, the goal of our project was to collect and systematize data regarding an impact assessment of the short-term noninvasive stimulation of the ABVN on the parameters of HRV. This study is registered at http://clinicaltrials.gov. Its unique identifier is NCT05680337.

2. Data Description

Our research was conducted at multiple institutions: (1) Bakulev National Medical Research Center for Cardiovascular Surgery; (2) Federal Center for Cardiovascular Surgery (Astrakhan); and (3) Research Institute of Ochapovsky Regional Clinical Hospital #1 (Krasnodar). This study's protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Russian Government.

The study was approved by the committees on human study participants of all the participating institutions and conducted according to the international standards of good clinical practice. Written informed consent was obtained from each patient prior to a randomization procedure. The design of the study is simple and pragmatic to maximize the possible practical application that can be extrapolated to real-world patients. The data were collected by all the authors and were received, verified, and analyzed at the Bakulev Center for Cardiovascular Surgery of the Russian Federation Ministry of Healthcare.

The parameters of HRV assessed in this study are presented in Table 1. Their physiological interpretation is not discussed in this article since it was specified in our previous publications [36–39]. In addition, the raw records of the rhythmograms of all the subjects in EDF format, as well as the dataset containing clinical, instrumental, and laboratory data of all the study subjects are available for possible secondary analysis to all interested researchers (2022 data, n = 71).

Table 1. HRV parameters.

Parameter (Acronym)	Description
HR	Heart rate
RRNN	Mean duration of RR intervals
NArr	Percentage of arrhythmias and artifacts
NN50	Number of NN intervals that differ from neighboring ones by more than 50 ms
pNN50	Number of pairs of cardiac time intervals with a difference of more than 50 ms, % of the total number of cardiac time intervals in the array
SDNN	Standard deviation of the array of normal cardiac intervals
D	Variance of the array of normal cardiac time intervals
MxDMn	Difference between the maximum and minimum values of normal cardiac intervals
MxRMn	Ratio of the maximum to the minimum value of the RR interval
RMSSD	Root mean square of the successive differences of cardiac time intervals
CV	Coefficient of variation of the complete array of cardiac time intervals
Mo	Mode
AMo	Mode amplitude, the percentage of cardiac time intervals corresponding to the mode value
IAB	Index of autonomic balance
IARP	Index of the adequacy of regulatory processes
APR	Autonomic rhythm index
IC1	Index of centralization (HF+LF)/VLF
IC2	Index of centralization (VHF+LF)/LF
SI	Stress index of regulatory systems
IARS	Index of the activity of regulatory systems
HF%	Relative power of the high-frequency oscillations in the heart rate spectrum (0.15 to 0.4 Hz)
LF%	Relative power of the low-frequency oscillations in the heart rate spectrum (0.04 to 0.15 Hz)
VLF%	Relative power of the very low-frequency oscillations in the heart rate spectrum (0.0033 to 0.04 Hz)
ULF%	Relative power of the ultra-low-frequency oscillations in the heart rate spectrum (0.0033 to 0.04 Hz)
TP	Total power of the entire heart rate spectrum
HF	Power of high-frequency oscillations in the heart rate spectrum, absolute value
LF	Power of low-frequency oscillations in the heart rate spectrum, absolute value
VLF	Power of very low-frequency oscillations in the heart rate spectrum, absolute value
ULF	Power of ultra-low-frequency oscillations in the heart rate spectrum, absolute value
LF/HF	Ratio the percentage contributions of the low-frequency to high-frequency oscillations in the heart rate spectrum

The dataset currently contains data on 71 patients. Their clinical, instrumental, and laboratory characteristics are presented in Tables S1 and S2. A comparative analysis of the studied HRV parameters at baseline and at all periods of the study is presented in Tables S3–S7.

3. Methods

The inclusion criterion for the study was the sinus rhythm of the prospective subject at the time of the experiment. All the patients were admitted to clinics for the purpose of diagnosis, and some were planned for surgical treatment. This contributed to the accuracy of our knowledge on the presence or absence of cardiac pathology in the prospective study participants based on invasive and noninvasive diagnostic procedures (echocardiography, coronary angiography, cardiac MRI, myocardial scintigraphy, etc.) and the results of laboratory diagnostic methods. In most earlier studies on the stimulation of the ABVN,

the authors used apparently healthy volunteers [40–44]. The latter are rarely examined by instrumental diagnostic methods, such as echocardiography or biochemical blood tests. Furthermore, they have no access to assessing the presence or absence of coronary artery lesions based on selective coronary angiography.

The exclusion criteria for the study were the following pathological conditions: frequent ventricular and/or supraventricular extrasystoles, atrioventricular block, glucocorticosteroid intake within the last month, intake of any antiarrhythmic medicines except for beta-blockers, and severe chronic pathology of the liver and kidney.

Our study subjects were randomly assigned to two groups (T as in tragus and E as in earlobe), using the envelope method, according to the scheme 1:1. The treatment group T received active stimulation of the ABVN (tragus), while the control group E received sham stimulation (earlobe). The study algorithm included four five-minute time intervals of biological signal records: (1) initially at rest, (2) during the first 5 min of stimulation, (3) during the subsequent 5 min of stimulation, and (4) after the end of stimulation. Thus, the total duration of stimulation was 10 min.

The study was conducted in the evening hours (5:00–6:00 p.m.) before eating, so that the possible influence of daily fluctuations and postprandial influences on the autonomic regulation of the cardiovascular system were excluded and monotonous conditions for all the patients were created. The registration of the studied signals took place in a specialized functional diagnostics room that adheres to the medical requirements for such offices (temperature 21–24 °C, required humidity, lighting, wall covering, etc.), in the presence of a research doctor, without unauthorized persons. The influence of various kinds of sounds, etc., were also excluded.

The following equipment was also in the room: a digital electrocardiograph ("BTL Flexi ECG", BTL, Newcastle, UK) and two Doppler echocardiographs (Sonoline Si-450, Siemens, Munich, Germany) (IE-33 Philips Medical Systems, Dallas, TX, USA). Of course, any electronic equipment located nearby could theoretically be the source of interference and noise. However, the equipment we use is legally certified in our country as medical equipment and can be used for medical purposes. In such devices, there are many methods of suppressing the influence of noise on the parameters of the studied signal.

All the patients were in a horizontal position at all points of the study. The first (initial, without stimulation) ECG recording was performed after the patient assumed a horizontal position for at least 10 min. During all the stages of the study, the patients' breathing was arbitrary.

Electrical stimulation was performed in all the subjects in the same way, with a frequency of 20 Hz and a pulse length of 200 μs. Electric current pulse strength (mA) was selected individually, depending on the pain perception of the subject: it was set to 1 unit below the pain threshold. An important point of the study was the mandatory use of an electrically conductive gel at the point of contact between the electrode and the subject's skin. This substantially reduced the electrical impedance of the skin and pain sensitivity, which contributed to the possibility of increasing the values of the electric current pulse strength and improved the tolerability of the procedure.

We used a Mercury stimulation device (Shenzhen Dongdixin Technology Co., Ltd., Shenzhen, China) ordered through STL (Moscow, Russia). The mode of operation was transcutaneous electrical nerve stimulation, low-frequency stimulation with bipolar (two-phase) rectangular electric current pulses. To record the biological signals, we employed a single-channel ECG recorder, Ritmer M1, with automatic calculation of the HRV parameters in the Ritmer web application (Biomedicine of the Future LLC, Moscow, Russia). We also used the medium viscosity gel Mediagel (Geltek-Medica LLC, Moscow, Russia) for ultrasound scan and therapy (Figure 1).

Figure 1. Devices for conducting the research.

Figure 2 presents the options of attaching a cardiac event recorder to a patient and an image of a single-channel ECG in the Ritmer web application. Figure 3 demonstrates how the percutaneous surface electrode was attached.

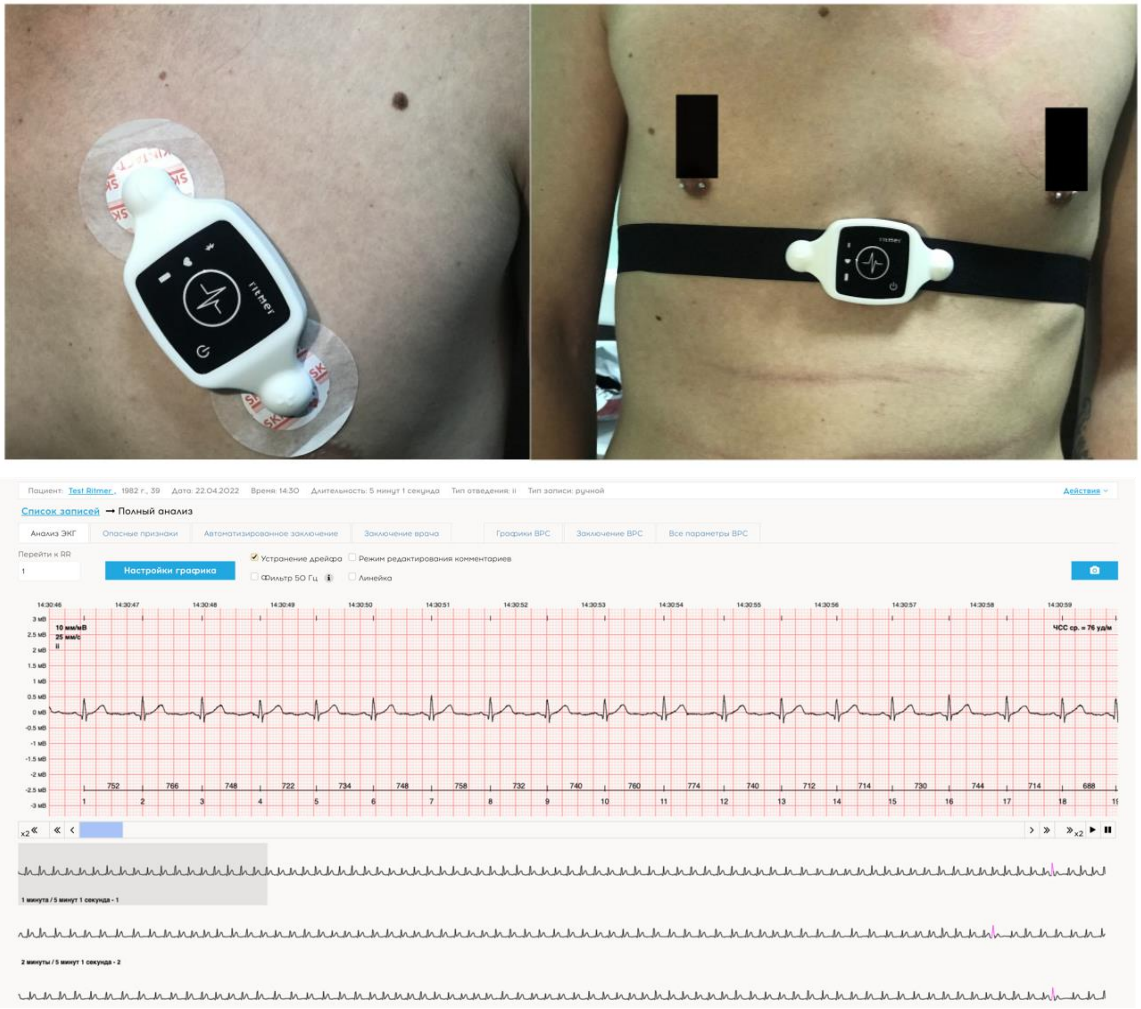

Figure 2. Options of attaching the cardiac event recorder to patients for ECG recording and the image of a single-channel ECG in the Ritmer device web application.

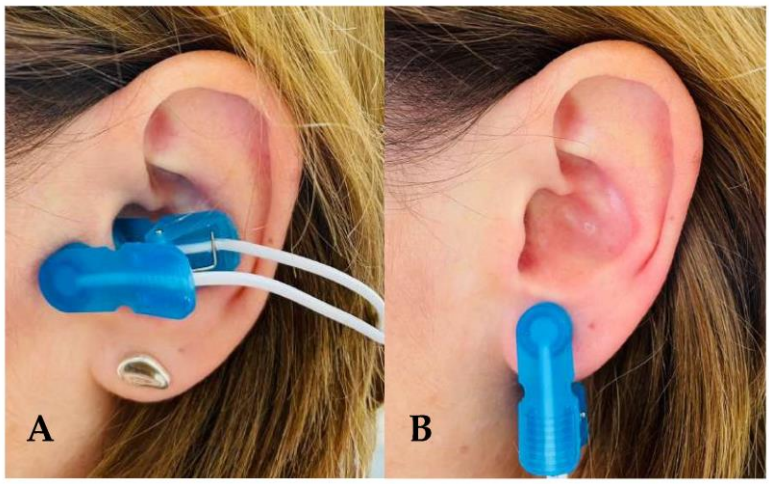

Figure 3. (**A**) Active stimulation of the auricular branch of the vagus nerve: tragus; (**B**) sham stimulation: earlobe.

4. User Notes

To obtain valid results, it is necessary to accumulate a larger array of records. In addition, systematization is important in future analysis. Given the fairly flexible inclusion and exclusion criteria, the cohort of study subjects will be quite heterogeneous. That is, the datasets will include, for example, patients with valvular heart disease, as well as patients with coronary atherosclerosis. It is logical that group-by-group analyses of these records will be more accurate and representative. With this goal in mind, we plan to accumulate records and perform their final analysis only when each group of patients reaches a sample size of roughly 300. This is a somewhat vague number, chosen empirically, with the expectation that it will be greater than the sum of all the subjects currently enrolled in experimental studies on the assessment of an auricular stimulation effect on HRV dynamics.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/data8050087/s1. Table S1: Clinical parameters of patients and drug therapy; Table S2: Instrumental and laboratory data of patients; Table S3: HRV parameters initially; Table S4: HRV parameters (first 5 min of stimulation); Table S5: HRV parameters (second 5 min of stimulation); Table S6: HRV parameters (after stimulation); Table S7: HRV parameters (after stimulation).

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Institutional Review Board Statement: This study was approved by the Ethics Committee of Bakulev Scientific Center for Cardiovascular Surgery (Protocol #13 of 8 February, 2022), the Ethics Committee of the Federal Center for Cardiovascular Surgery of the Russian Federation Ministry of Healthcare, Astrakhan (Protocol #2 of 6 April 2022), and the Ethics Committee of the State Budgetary Public Health Institution, Ochapovsky Regional Clinical Hospital #1 (Protocol #4 of 20 April 2022).

Informed Consent Statement: Written informed consent was obtained from each patient prior to randomization.

Data Availability Statement: The datasets analyzed during the current study are publicly available. The data are available in the general repository, "*Open Science Framework*" at: https://doi.org/10.17605/OSF.IO/STU62.

Conflicts of Interest: The authors declare no potential conflict of interest relevant to the study.

References

1. Asconapé, J.J.; Moore, D.D.; Zipes, D.P.; Hartman, L.M.; Duffell, W.H., Jr. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: A rare complication of intraoperative device testing. *Epilepsia* **1999**, *40*, 1452–1454. [CrossRef] [PubMed]
2. Liu, A.; Rong, P.; Gong, L.; Song, L.; Wang, X.; Li, L.; Wang, Y. Efficacy and safety of treatment with transcutaneous vagus nerve stimulation in 17 patients with refractory epilepsy evaluated by electroencephalogram, seizure frequency, and quality of life. *Med. Sci. Monit.* **2018**, *24*, 8439–8448. [CrossRef] [PubMed]
3. Rong, P.; Liu, A.; Zhang, J.; Wang, Y.; Yang, A.; Li, L.; Ben, H. An alternative therapy for drug-resistant epilepsy: Transcutaneous auricular vagus nerve stimulation. *Chin. Med. J.* **2014**, *127*, 300–304. [PubMed]
4. Fang, J.; Egorova, N.; Rong, P. Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression. *Neuroimage Clin.* **2017**, *14*, 105–111. [CrossRef] [PubMed]
5. Rong, P.; Liu, J.; Wang, L.; Liu, R.; Fang, J.; Zhao, J.; Zhao, Y.; Wang, H. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. *J. Affect. Disord.* **2016**, *195*, 172–179. [CrossRef]
6. Gaul, C.; Diener, H.-C.; Silver, N.; Magis, D.; Reuter, U.; Andersson, A.; Liebler, E.J. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study. *Cephalalgia* **2016**, *36*, 534–546. [CrossRef]
7. Hyvärinen, P.; Yrttiaho, S.; Lehtimäki, J.; Ilmoniemi, R.J.; Mäkitie, A.; Ylikoski, J.; Mäkelä, J.P.; Aarnisalo, A.A. Transcutaneous vagus nerve stimulation modulates tinnitus-related beta- and gamma-band activity. *Ear Hear.* **2015**, *36*, e76–e85. [CrossRef]
8. De Ferrari, G.M.; Crijns, H.J.; Borggrefe, M.; Milasinovic, G.; Smid, J.; Zabel, M.; Gavazzi, A.; Sanzo, A.; Dennert, R.; Kuschyk, J.; et al. Chronic vagus nerve stimulation: A new and promising therapeutic approach for chronic heart failure. *Eur. Heart J.* **2011**, *32*, 847–855. [CrossRef]
9. Pavlyukova, E.N.; Kuz'michkina, M.A.; Afanasiev, S.A.; Karpov, R.S. Auricular vagal stimulation in the treatment of patients with left ventricular dysfunction. *Klin. Med.* **2013**, *91*, 27–31.
10. Wang, Z.; Zhou, X.; Sheng, X.; Yu, L.; Jiang, H. Unilateral low-level transcutaneous electrical vagus nerve stimulation: A novel noninvasive treatment for myocardial infarction. *Int. J. Cardiol.* **2015**, *190*, 9–10. [CrossRef]
11. Hasan, A.; Wolff-Menzler, C.; Pfeiffer, S.; Falkai, P.; Weidinger, E.; Jobst, A.; Wobrock, T. Transcutaneous noninvasive vagus nerve stimulation (tVNS) in the treatment of schizophrenia: A bicentric randomized controlled pilot study. *Eur. Archiv. Psychiatry Clin. Neurosci.* **2015**, *265*, 589–600. [CrossRef] [PubMed]
12. Keute, M.; Boehrer, L.; Ruhnau, P.; Heinze, H.-J.; Zaehle, T. Transcutaneous vagus nerve stimulation (tVNS) and the dynamics of visual bistable perception. *Front. Neurosci.* **2019**, *13*, 227. [CrossRef] [PubMed]
13. Drapkina, O.M.; Dzhioeva, O.N.; Rogozhkina, E.A.; Shvarts, E.N.; Kiselev, A.R. Percutaneous non-invasive stimulation: Possibilities and prospects of the method in the practice of specialists in internal diseases. *Complex Issues Cardiovasc. Dis.* **2022**, *11*, 191–200. [CrossRef]
14. Kiselev, A.R.; Schwartz, E.N.; Dzhioeva, O.N.; Drapkina, O.M. Physiological basis of obesity treatment by percutaneous vagus nerve stimulation. *Profil. Meditsina* **2022**, *25*, 111–115. [CrossRef]
15. Ben-Menachem, E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol.* **2002**, *1*, 477–482. [CrossRef]
16. Johnson, R.L.; Wilson, C.G. A review of vagus nerve stimulation as a therapeutic intervention. *J. Inflamm. Res.* **2018**, *11*, 203–213. [CrossRef] [PubMed]
17. Fahy, B.G. Intraoperative and perioperative complications with a vagus nerve stimulation device. *J. Clin. Anesth.* **2010**, *22*, 213–222. [CrossRef]
18. Mertens, A.; Raedt, R.; Gadeyne, S.; Carrette, E.; Boon, P.; Vonck, K. Recent advances in devices for vagus nerve stimulation. *Expert Rev. Med. Devices* **2018**, *15*, 527–539. [CrossRef] [PubMed]
19. Kaniusas, E.; Kampusch, S.; Tittgemeyer, M.; Panetsos, F.; Gines, R.F.; Papa, M.; Széles, J.C. Current Directions in the Auricular Vagus Nerve Stimulation I—A Physiological Perspective. *Front. Neurosci.* **2019**, *13*, 854. [CrossRef]
20. Kaniusas, E.; Samoudi, A.M.; Kampusch, S.; Bald, K.; Tanghe, E.; Martens, L.; Joseph, W.; Széles, J.C. Stimulation Pattern Efficiency in Percutaneous Auricular Vagus Nerve Stimulation: Experimental Versus Numerical Data. *IEEE Trans. Biomed. Eng.* **2020**, *67*, 1921–1935. [CrossRef]
21. Murray, A.R.; Atkinson, L.; Mahadi, M.K.; Deuchars, S.A.; Deuchars, J. The strange case of the ear and the heart: The auricular vagus nerve and its influence on cardiac control. *Auton. Neurosci.* **2016**, *199*, 48–53. [CrossRef] [PubMed]
22. He, W.; Wang, X.; Shi, H.; Zhang, H.; Li, L.; Jing, X.; Zhu, B. Auricular acupuncture and vagal regulation. *Evid. Based Complement. Altern. Med.* **2012**, *2012*, 786839. [CrossRef] [PubMed]
23. Ardell, J.L.; Randall, W.C. Selective vagal innervation of sinoatrial and atrioventricular nodes in canine heart. *Am. J. Physiol.* **1986**, *251 Pt 2*, H764–H773. [CrossRef] [PubMed]

24. Krahl, S. Vagus nerve stimulation for epilepsy: A review of the peripheral mechanisms. *Surg. Neurol. Int.* **2012**, *3* (Suppl. S1), 47–52. [CrossRef] [PubMed]
25. Capilupi, M.J.; Kerath, S.M.; Becker, L.B. Vagus Nerve Stimulation and the Cardiovascular System. *Cold Spring Harb. Perspect. Med.* **2020**, *10*, a034173. [CrossRef] [PubMed]
26. Antonino, D.; Teixeira, A.L.; Maia-Lopes, P.M.; Souza, M.C.; Sabino-Carvalho, J.L.; Murray, A.R.; Vianna, L.C. Non-invasive vagus nerve stimulation acutely improves spontaneous cardiac baroreflex sensitivity in healthy young men: A randomized placebo-controlled trial. *Brain Stimul.* **2017**, *10*, 875–881. [CrossRef]
27. Clancy, J.A.; Mary, D.A.; Witte, K.K.; Greenwood, J.P.; Deuchars, S.A.; Deuchars, J. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul.* **2014**, *7*, 871–877. [CrossRef] [PubMed]
28. Tran, N.; Asad, Z.; Elkholey, K.; Scherlag, B.J.; Po, S.S.; Stavrakis, S. Autonomic neuromodulation acutely ameliorates left ventricular strain in humans. *J. Cardiovasc. Trans. Res.* **2019**, *12*, 221–230. [CrossRef]
29. Lamb, D.G.; Porges, E.C.; Lewis, G.F.; Williamson, J.B. Non-invasive vagal nerve stimulation effects on hyperarousal and autonomic state in patients with posttraumatic stress disorder and history of mild traumatic brain injury: Preliminary evidence. *Front. Med.* **2017**, *4*, 124. [CrossRef]
30. Borges, U.; Laborde, S.; Raab, M. Influence of transcutaneous vagus nerve stimulation on cardiac vagal activity: Not different from sham stimulation and no effect of stimulation intensity. *PLoS ONE* **2019**, *14*, e0223848. [CrossRef]
31. Burger, A.M.; Van der Does, W.; Thayer, J.F.; Brosschot, J.F.; Verkuil, B. Transcutaneous vagus nerve stimulation reduces spontaneous but not induced negative thought intrusions in high worriers. *Biol. Psychol.* **2019**, *142*, 80–89. [CrossRef] [PubMed]
32. Burger, A.M.; Van Diest, I.; Van der Does, W.; Korbee, J.N.; Waziri, N.; Brosschot, J.F.; Verkuil, B. The effect of transcutaneous vagus nerve stimulation on fear generalization and subsequent fear extinction. *Neurobiol. Learn. Mem.* **2019**, *161*, 192–201. [CrossRef] [PubMed]
33. Teckentrup, V.; Neubert, S.; Santiago, J.C.P.; Hallschmid, M.; Walter, M.; Kroemer, N.B. Non-invasive stimulation of vagal afferents reduces gastric frequency. *Brain Stimul.* **2020**, *13*, 470–473. [CrossRef] [PubMed]
34. Wolf, V.; Kühnel, A.; Teckentrup, V.; Koenig, J.; Kroemer, N.B. Does transcutaneous auricular vagus nerve stimulation affect vagally mediated heart rate variability? A living and interactive Bayesian meta-analysis. *Psychophysiology* **2021**, *58*, e13933. [CrossRef] [PubMed]
35. Farmer, A.D.; Strzelczyk, A.; Finisguerra, A.; Gourine, A.V.; Gharabaghi, A.; Hasan, A.; Koenig, J. International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020). *Front. Hum. Neurosci.* **2021**, *14*, 568051. [CrossRef]
36. Huikuri, H.V.; Stein, P.K. Heart rate variability in risk stratification of cardiac patients. *Prog. Cardiovasc. Dis.* **2013**, *56*, 153–159. [CrossRef]
37. Togo, F.; Takahashi, M. Heart rate variability in occupational health—A systematic review. *Ind. Health* **2009**, *47*, 589–602. [CrossRef] [PubMed]
38. Benichou, T.; Pereira, B.; Mermillod, M.; Tauveron, I.; Pfabigan, D.; Maqdasy, S.; Dutheil, F. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS ONE* **2018**, *13*, e0195166. [CrossRef]
39. Shvartz, V.A.; Kiselev, A.R.; Karavaev, A.S.; Vulf, K.A.; Borovkova, E.I.; Prokhorov, M.D.; Petrosyan, A.D.; Bockeria, O.L. Comparative study of short-term cardiovascular autonomic control in cardiac surgery patients who underwent coronary artery bypass grafting or correction of valvular heart disease. *J. Cardiovasc. Thorac. Res.* **2018**, *10*, 28–35. [CrossRef]
40. De Icco, R.; Martinelli, D.; Bitetto, V.; Fresia, M.; Liebler, E.; Sandrini, G.; Tassorelli, C. Peripheral vagal nerve stimulation modulates the nociceptive withdrawal reflex in healthy subjects: A randomized, cross-over, sham-controlled study. *Cephalalgia* **2018**, *38*, 1658–1664. [CrossRef]
41. De Couck, M.; Cserjesi, R.; Caers, R.; Zijlstra, W.P.; Widjaja, D.; Wolf, N.; Luminet, O.; Ellrich, J.; Gidron, Y. Effects of short and prolonged transcutaneous vagus nerve stimulation on heart rate variability in healthy subjects. *Auton. Neurosci.* **2017**, *203*, 88–96. [CrossRef] [PubMed]
42. Murray, A.R.; Clancy, J.A.; Deuchars, S.A.; Deuchars, J. Transcutaneous vagus nerve stimulation (tVNS) decreases sympathetic nerve activity in older healthy human subjects. *Heart* **2016**, *102*, A142. [CrossRef]
43. Tobaldini, E.; Toschi-Dias, E.; Appratto de Souza, L.; Rabello Casali, K.; Vicenzi, M.; Sandrone, G.; Montano, N. Cardiac and Peripheral Autonomic Responses to Orthostatic Stress During Transcutaneous Vagus Nerve Stimulation in Healthy Subjects. *J Clin. Med.* **2019**, *8*, 496. [CrossRef] [PubMed]
44. Paleczny, B.; Seredyński, R.; Ponikowska, B. Inspiratory- and expiratory-gated transcutaneous vagus nerve stimulation have different effects on heart rate in healthy subjects: Preliminary results. *Clin. Auton. Res.* **2021**, *31*, 205–214. [CrossRef] [PubMed]