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Bionic Autonomic Neuromodulation Revolutionizes Cardiology in the 21st Century

Kenji Sunagawa, *Senior Member, IEEE*

Abstract — **In this invited session, we would like to address the impact of bionic neuromodulation on cardiovascular diseases. It has been well established that cardiovascular dysregulation plays major roles in the pathogenesis of cardiovascular diseases. This is the reason why most drugs currently used in cardiology have significant pharmacological effects on the cardiovascular regulatory system. Since the ultimate center for cardiovascular regulation is the brainstem, it is conceivable that autonomic neuromodulation would have significant impacts on cardiovascular diseases. On the basis of this framework, we first developed a bionic, neurally regulated artificial pacemaker. We then substituted the brainstem by CPU and developed a bionic artificial baroreflex system. We further developed a bionic brain that achieved better regulatory conditions than the native brainstem in order to improve survival in animal model with heart failure. We recently developed a bionic neuromodulation system to reduce infarction size following acute myocardial infarction. We believe that the bionic neuromodulation will inspire even more intricate applications in cardiology in the 21st century.**

I. OVERVIEW OF PREVIOUIS BIONIC STUDIES

In the human body, all cells, tissues, organs, and systems operate coherently. The presence of well-developed neurohormonal communications among these components of the body is the essential infrastructure that makes coherent functioning possible. If we could incorporate such communication mechanisms into artificial systems, they would function as if they are an integral part of the corresponding native physiological systems. We call such well-integrated artificial systems bionic systems.

The bread-and-butter technology that is common to all bionic systems is the technique for interfacing with the native systems, in particular, the human body's regulatory systems. Unification of an artificial system with a native system requires bidirectional communications. In 1995, we developed one such system, a neurally regulated artificial pacemaker [1]. Physiological studies indicated that the instantaneous sinus rate was determined not only by the current sympathetic activity but also by the history of sympathetic activity. We quantified its history dependence by the impulse response of the sinus rate to sympathetic stimulation. Using the convolution integral of the impulse response with the instantaneous sympathetic activity, we could predict the precise sinus rate in real time [1].

The success of the neurally regulated bionic pacemaker has convinced us that the autonomic system can be effectively monitored and thereby manipulated by bionic systems. The clinical impact of direct manipulation of autonomic functions in cardiovascular diseases is very profound. The case of central baroreflex failure is an archetypal example of one such application. In treating this disease, it is conceivable that one can implement an artificial bionic baroreflex system as a kind of biological proxy capable of emulating the native central baroreflex function of the failing vasomotor center. The bionic baroreflex system consists of a pressure sensor (baroreceptor), microprocessor (vasomotor center) and nerve stimulator (for activation of sympathetic efferents). The system operates as an intelligent negative feedback regulator, and has been demonstrated in animals and patients to be effective in restoring normal baroreflex functioning [2-5].

Recently, we developed an artificial brain stem that takes over the native cardiac regulation, and optimized it to improve the survival of chronic heart failure [6]. Two weeks after the ligation of the left coronary artery in rats, surviving animals were randomized to vagal- and sham-stimulated groups. Vagal stimulation markedly improved the 140-day survival (86% versus 50%, P=0.008). The relative risk reduction of death reached over 70%. The success of the bionic treatment of heart failure opens up an entirely new therapeutic paradigm for patients with chronic heart failure.

II. BIONIC NEUROMODULATION IN ISCHEMIA

Although the bionic autonomic neuromodulation system prevented progression, thereby improved survival of chronic heart failure, it would be far desirable if we can prevent the development of heart failure. Ischemic heart disease has been known as one of the major causes of heart failure. Therefore, we examined whether bionic autonomic neuromodulation impacts ischemia-reperfusion injury of the heart. This particular application of bionic autonomic neuromodulation is critically important under clinical settings because early reperfusion of occluded coronary arteries has become a standard therapy worldwide.

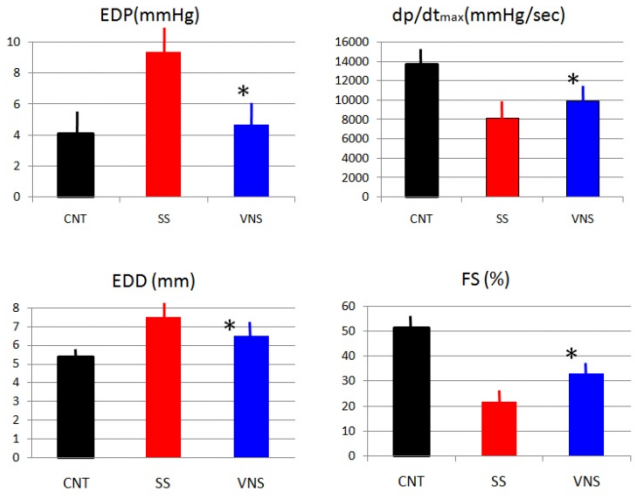
Myocardial infarction has been known to augment sympathetic afferent traffic and reduce vagal efferent activity. We investigated whether short-term electrical stimulation of

the vagal nerve could ameliorate cardiac dysfunction in a distant period after ischemia-reperfusion injury.

Ischemia-reperfusion injury model was created in Sprague-Dawley rats by ligating the left coronary artery for 30 min followed by reperfusion. We stimulated the right vagal nerve (the stimulation condition is proprietary) from the onset of ischemia for 3 hrs. We measured hemodynamics before ischemia, 4 days after ischemia with and without bionic autonomic neuromodulation. We estimated left ventricular function using echocardiography. We estimated infarction size histologically 4 days after ischemia.

III. RESULTS

As shown in the upper panels of figure, in comparison with sham stimulation (SS, n=6), vagal nerve stimulation (VNS, n=6) significantly decreased left ventricular end-diastolic pressure, and increased left ventricular (dp/dt)max suggesting improved left ventricular function. CNT represents the control condition (n=4). The improvement of left ventricular function was paralleled with decreased end-diastolic dimension (EDD), and increased shortening fraction (EF) as shown in the lower panels in the figure. Histological examination further supported the notion that vagal stimulation decreased the infarction size (33±5% vs. 24±3%, p<.01). Biochemical analysis indicated that vagal stimulation downregulated mRNA of procollagens, such as Col1a1, Col3a1, and Ctgf, in infarcted myocardium. Therefore, the positive impact of vagal nerve stimulation might have, at least in part, resulted from inhibition of collagen production in ischemia-reperfusion injury.



IV. DISCUSSION

We have shown that vagal stimulation early after the creation of ischemia resulted in marked reduction in infarction size and improvement of left ventricular function with attenuated cardiac remodeling. Although the effect of vagal nerve stimulation on long term survival remains to be investigated, it is conceivable that the vagal nerve stimulation early after ischemia-reperfusion injury may have a positive impact on such a hard endpoint.

The mechanism by which the bionic neuromodulation improves ischemia-reperfusion injury remains unknown. The bradycardiac effect of vagal stimulation might be a contributing factor. However, our pilot study indicated that a comparable heart rate reduction induced by beta-blocker failed to show the positive impacts on ischemia-reperfusion injury as much as the vagal stimulation did. Theretofore, mechanisms other than the bradycardiac effect such as energy sparing effect, anti-inflammatory effect and anti-oxidant effect need to be considered [7-10].

V. CONCLUSION

Vagal nerve stimulation reduces infarct size, improves left ventricular function and attenuates left ventricular remodeling after ischemia-reperfusion injury. Bionic autonomic neuromodulation should inspire even more intricate applications in cardiology in the 21st century.

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