33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Artificial Baroreflex System Restores Volume Tolerance in the Absence of Native Baroreflex

Kazuya Hosokawa, Kouta Funakoshi, Atsushi Tanaka, Takafumi Sakamoto, Ken Onitsuka, Kazuo Sakamoto, Tomoyuki Tobushi, Takeo Fujino, Keita Saku, Yoshinori Murayama, Tomomi Ide and Kenji Sunagawa, *Senior Member, IEEE*

***Abstract*— The arterial baroreflex stabilizes arterial pressure by modulating the mechanical properties of cardiovascular system. We previously demonstrated that the baroreflex impairment makes the circulatory system extremely sensitive to volume overload and predisposes to pulmonary edema irrespective of left ventricular systolic function. To overcome the volume intolerance, we developed an artificial baroreflex system by directly stimulating the carotid sinus nerves in response to changes in arterial pressure. The artificial baroreflex system precisely reproduced the native arterial pressure response and restored physiological volume buffering function. We conclude that the artificial baroreflex system would be an attractive tool in preventing pulmonary edema in patients with impaired baroreflex function.**

I. Introduction

Heart failure is a major medical problem worldwide. Although latest therapeutic strategy benefits many patients with heart failure, their prognosis remains unacceptably poor [1]. We demonstrated that baroreflex failure induces volume intolerance and predisposes to pulmonary edema irrespective of left ventricular systolic function. At present, no therapeutic strategy to restore baroreflex function is available. The aim of this study is to develop an artificial baroreflex system capable of restoring volume buffering function.

Manuscript received April 15, 2011. This work was supported in part by Health and Labour Sciences Research Grant for Research on Medical Devices for Improving Impaired QOL from the Ministry of Health Labour and Welfare of Japan, Health and Labour Sciences Research Grant for Clinical Research from the Ministry of Health Labour and Welfare of Japan, and Grant-in-Aid for Scientific Research(S) (18100006） from the Japan Society for the Promotion of Science

Authors are with Kyushu University Graduate School of Medical Sciences, Department of Cardiovascular Medicine. 8128582 Higashi-ku, Maidashi 3-1-1, Fukuoka, Japan (corresponding author K. Hosokawa to provide phone: +81-92-642-5360; fax: +81-92-642-5357; e-mail: ncvchoso@cardiol.med.kyushu-u.ac.jp).

II. Methods

Surgical Preparations

The care and use of the animals were strict accordance with the guiding principles of our institution. In 14 anesthetized Sprague-Dawley rats weighing 562±37g, the baroreceptor regions were vascularily isolated [2]. The intra-carotid sinus pressure (CSP) was controlled by a servo-controlled piston pump (ET-126A and PA-119; Labworks, Costa Mesa, CA). Bilateral aortic depressor nerves were cut and a pair of electrodes was attached to the proximal end of the aortic depressor nerves for stimulation.

Framework of the artificial baroreflex system

As shown in Fig. 1, the artificial baroreflex system consisted of a pressure sensor, regulator and neuro-stimulator. The operating rule (H_{ABS}), how the regulator translates arterial pressure (AP) into stimulation (STM), was identified by the ratio of transfer functions from CSP to AP ($H_{CSP\text{-}AP}$) to that from STM to AP ($H_{STM\text{-}AP}$). To obtain $H_{CSP\text{-}AP}$ and $H_{STM\text{-}AP}$, we perturbed CSP and the pulse frequency of the neuro-stimulation with random binary sequences (Data were not shown).

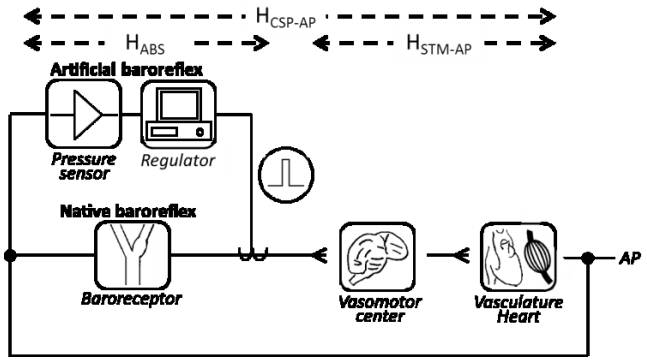

Fig. 1: Framework of artificial baroreflex system

A. Protocol-1: Comparison of open-loop pressure regulation between the native baroreflex and artificial baroreflex system

We implemented identified H_{ABS} into the regulator. Under the open loop condition (Fig. 2), we alternatively imposed pressure changes stepwise into CSP and the pressure sensor of the artificial baroreflex system. We then compared the arterial pressure responses.

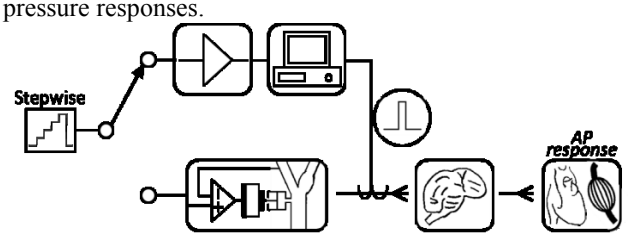

Fig. 2: Comparison of open-loop pressure regulation between the native baroreflex and artificial baroreflex system (Protocol -1)

B. Protocol-2: Comparison of volume buffering function between the native baroreflex and artificial baroreflex system

Under the closed loop condition of the native or artificial baroreflex system (Fig. 3), in order to examine the volume buffering function, we infused dextran stepwise and measured left atrial pressure (LAP) every 1 minute until LAP reaches 11mmHg. We plotted the LAP-infused volume relationships.

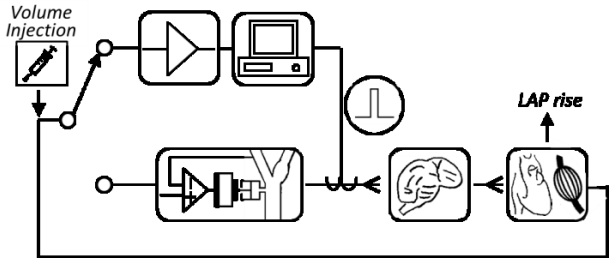

Fig. 3: Comparison of volume buffering function between the native baroreflex and artificial baroreflex system (Protocol-2)

III. RESULTS

Identification of the H_{ABS}

Both H_{CSP-AP} and H_{STM-AP} showed the characteristics of lowpass filter with similar corner frequencies. Taking the ratio of H_{CSP-AP} to H_{STM-AP} yielded H_{ABS} (Data were not shown).

A. Protocol-1: Comparison of open-loop pressure regulation between the native baroreflex and artificial baroreflex system

The arterial pressure responses between the native baroreflex and artificial baroreflex system were indistinguishable (Fig. 4). Maximal gain was -2.28±0.88 in the native baroreflex and was -2.20±1.18 (NS, n=7) in the artificial baroreflex system.

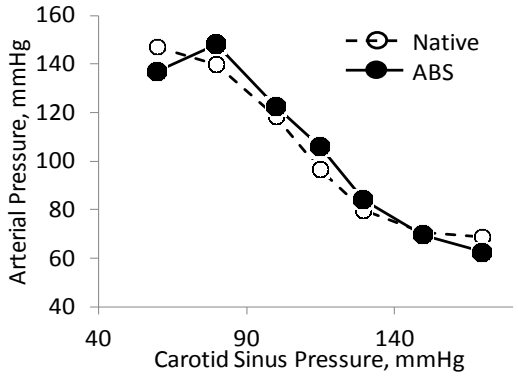

Fig. 4: The artificial baroreflex system reproduces the native baroreflex function

B. Protocol-2: Comparison of volume buffering function between the native baroreflex and artificial baroreflex system

In comparison with no baroreflex, the native baroreflex markedly buffered the increase in LAP in response to volume infusion. The artificial baroreflex system was as powerful as the native baroreflex in buffering the increase in LAP to volume infusion (Fig. 5).

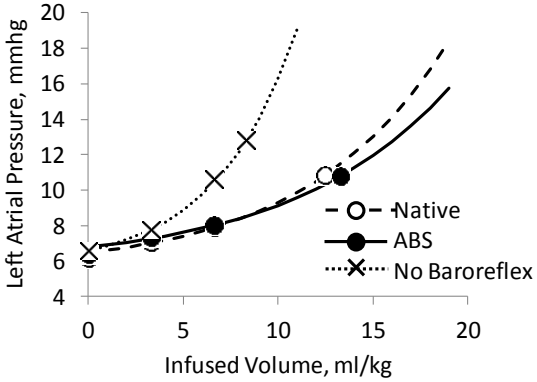

Fig. 5: The artificial baroreflex system restores normal volume buffering function

IV. DISCUSSION

We have shown that the artificial baroreflex system reproduced the open-loop characteristics of baroreflex pressure regulation reasonably well including the saturation and threshold effects of native baroreflex (Fig. 4). Since electrical stimulation of the carotid sinus nerves is linearly dependent on input arterial pressure (CSP), the reproduction of the nonlinear pressure responses would like to reflect the nonlinear sympathetic activation by the central mechanism.

The artificial baroreflex system restored physiological volume buffering function (Fig. 5). We estimated the amount of volume required to induce pulmonary edema by fitting the LAP-infused volume relationship to a monoexponential curve. We defined the critical volume load (critical ΔV) at which LAP reaches 18mmHg. The critical volume was 21.0±3.0ml/kg in the artificial baroreflex system and 20.1±3.0ml/kg in the native baroreflex, compared with 16.6± 4.4ml/kg in no baroreflex. The critical ΔV was markedly increased in normal baroreflex and in the artificial baroreflex system.

V. CONCLUSION

The artificial baroreflex system fully restored volume buffering function as well as arterial pressure regulation. The artificial baroreflex system would be an attractive therapeutic tool in preventing pulmonary edema in the presence of baroreflex failure irrespective of left ventricular systolic function. In order to develop a clinically useful system, further inventions in developing durable pressure sensors and electrodes are essential [3].

ACKNOWLEDGMENT

This study was supported in part by Health and Labour Sciences Research Grant for Research on Medical Devices for Improving Impaired QOL from the Ministry of Health Labour and Welfare of Japan, Health and Labour Sciences Research Grant for Clinical Research from the Ministry of Health Labour and Welfare of Japan, and Grant-in-Aid for Scientific Research(S) (18100006 ） from the Japan Society for the Promotion of Science.

REFERENCES

[1] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England journal of medicine. 2006;355(3):251-259.

[2] Sato T, Kawada T, Miyano H, Shishido T, Inagaki M, Yoshimura R, Tatewaki T, Sugimachi M, Alexander J, Jr., Sunagawa K. New simple methods for isolating baroreceptor regions of carotid sinus and aortic depressor nerves in rats. The American journal of physiology. 1999;276(1 Pt 2):H326-332.

[3] Sugimachi M, Sunagawa K. Bionic Cardiology: Exploration Into a Wealth of Controllable Body Parts in the Cardiovascular System. IEEE REVIEWS IN BIOMEDICAL ENGINEERING. 2009:2:172-186.