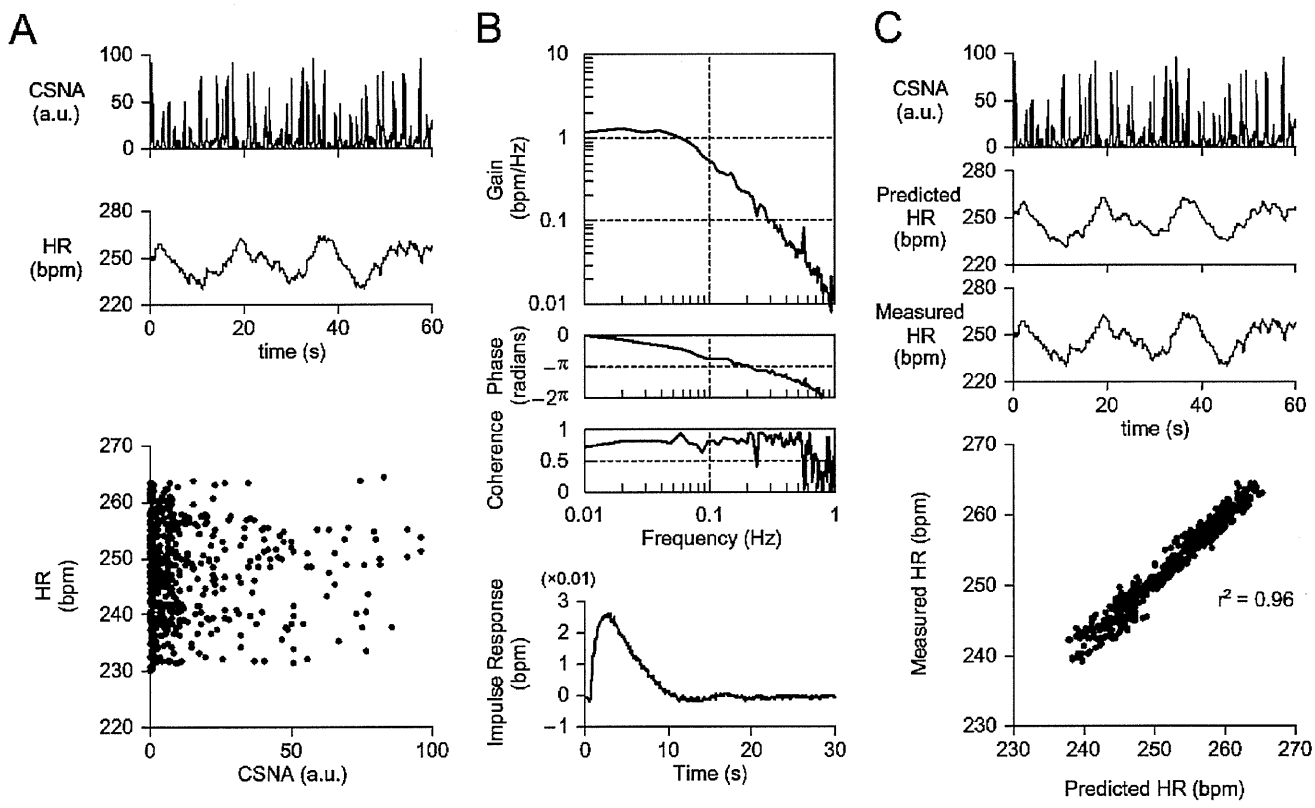

Fig. 1. A representative example of bionic cardiac pacemaker, i.e., neurally regulated pacemaker in a rabbit. (A) Simultaneously measured cardiac sympathetic nerve activity (CSNA) and heart rate (HR). Simple scattergram identified no obvious relationship. (B) Identified linear transfer function and corresponding impulse response to be used for decoding CSNA. (C) Decoded HR (predicted HR) from CSNA correlated well with measured HR. (Reproduced from [1] with permission.)

II. Treatment of Angina Pectoris

Angina pectoris is one form of ischemic cardiac diseases. This may manifest as a chronic stable form for years. Destabilization of atherosclerotic plaques may precipitate acute myocardial infarction resulting in irreversible myocardial loss. In unstable angina, there is an imbalance between oxygen supply and demand and an absolute shortage of coronary blood flow. In the stable form, however, the anginal attack occurs as a result of demand ischemia, usually associated with exertion, emotional stress, and exposure to cold environment. Therefore, a reduction in oxygen demand benefits patients with stable angina. In fact, antianginal drugs such as nitrates and beta-adrenergic blockers are believed to relieve angina by reducing oxygen demand.

A. Carotid Sinus Nerve Stimulation

The treatment of angina by neural intervention was first performed by manual massage of the carotid sinus [15], where the mechanoreceptor exists to feedback-control the autonomic tone. In 1967, Braunwald *et al.* [16] electrically stimulated carotid sinus nerves in two patients with angina, in the same year as Schwartz *et al.* [17] did in patients with hypertension. They used radio-frequency (RF)-coupled neurostimulators. Briefly, the implanted part of the device consisted of two pairs of bipolar platinum electrodes (for bilateral stimulation), coiled stainless steel leads, and a receiver unit. An external battery-driven transmitter delivered RF impulses transcutaneously through an antenna placed just above the receiver.

Carotid sinus nerve stimulation reflexly inhibits sympathetic activity and decreases myocardial oxygen consumption by lowering blood pressure, heart rate, and contractility. Enhanced vagal activity decreases heart rate and may directly decrease contractility [18] in the presence of a high sympathetic tone. Braunwald's group reported that on-demand use of carotid sinus nerve stimulation almost instantly aborted existing anginal attack and prevented the occurrence of new ones [16], [19]. Mason *et al.* [20] compared the effects of nitrates, beta-blockers, and carotid sinus nerve stimulation. Carotid sinus nerve stimulation was considered to reduce preload (as nitrates) and have negative chronotropic and inotropic (as beta-blockers) effects. Vatner *et al.* [19], [21] demonstrated in chronically instrumented conscious dogs that carotid sinus nerve stimulation lowered the resistance of various vascular beds. Of note, coronary vascular resistance also decreased while oxygen demand decreased and was considered to be mediated by sympathetic withdrawal. Solti *et al.* [22], [23] observed that carotid sinus nerve stimulation preferentially increased blood flow in ischemic areas. They attributed this observation to vasodilatation of collateral vessels.

In 1969, Epstein *et al.* [24], [25] treated 17 patients with drug-resistant angina using carotid sinus nerve stimulation. They observed symptomatic relief in 13 of their patients. Angina-interruptive and -prophylactic use of carotid sinus nerve stimulation prolonged exercise duration in 10 and 12, respectively, of the 13 patients. Carotid sinus stimulation had transient adverse effects (pain, cough, paresthesis, and neck tightness sensation; only for around four weeks) that were milder than those

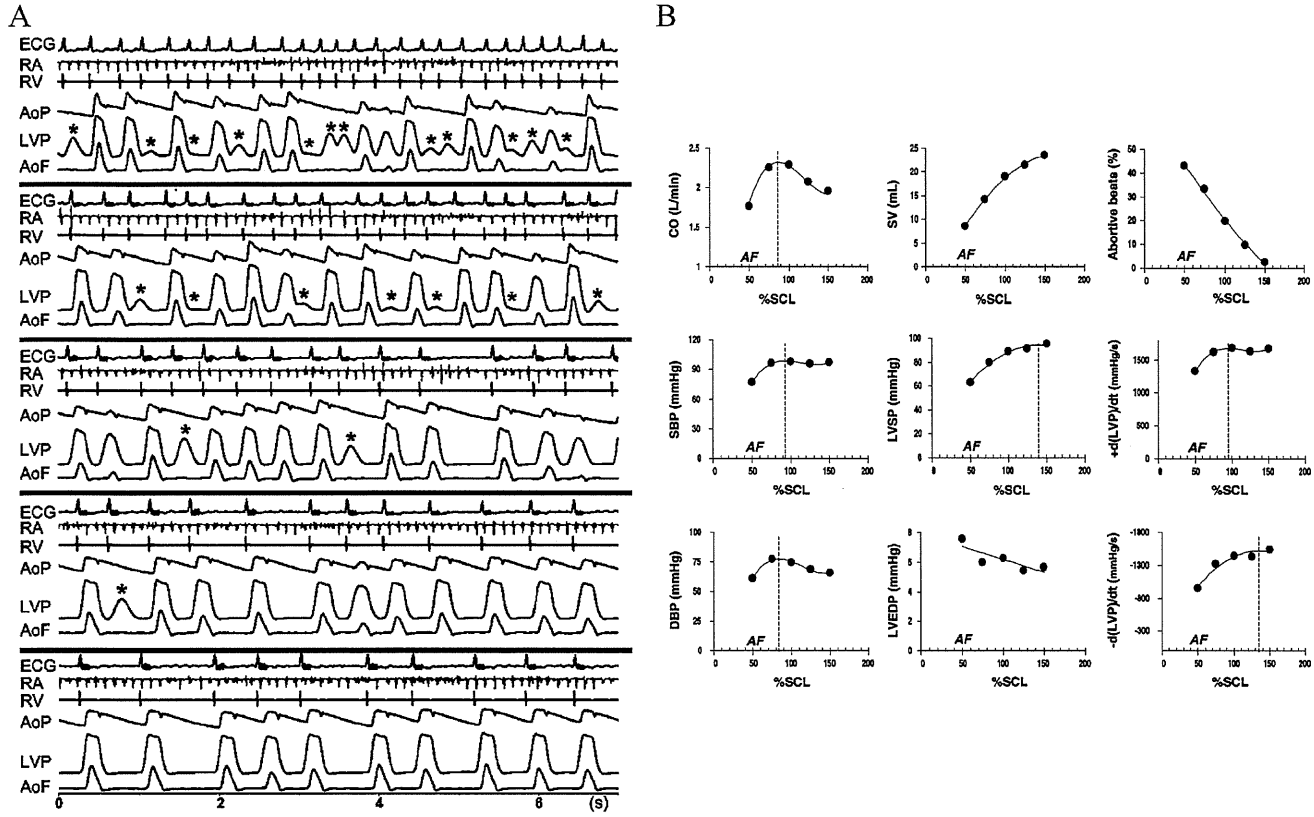

Fig. 2. (A) A representative example of controlling ventricular rate in a dog with atrial fibrillation (AF) by electrical stimulation of vagal nerve at epicardial fat pad innervating atrioventricular node. From top: no control, control to 75%, 100%, 125%, 150% of sinus cycle length (SCL). RA: intracardiac ECG from RA; RV: intracardiac ECG from RV; AoP: aortic pressure; LVP: left ventricular pressure; AoF: aortic flow; (*) abortive beats. (B) Effects of ventricular rate control by fat pad stimulation on hemodynamics in ten dogs. CO: cardiac output; SBP: systolic blood pressure; DBP: diastolic blood pressure; SV: stroke volume; LVSP: left ventricular systolic pressure; LVEDP: left ventricular end-diastolic pressure; $+\mathrm{d(LVP)/dt}$, maximal rate of rise in left ventricular pressure; $-\mathrm{d(LVP)/dt}$, minimal rate of fall in left ventricular pressure. (Reproduced from [33] with permission.)

of vagal stimulation (vomiting, salivation, coughing) [19], [26]. Detailed surgical techniques for carotid sinus stimulation have been described [19], [26]. Carotid sinus nerve stimulation was performed in various institutes worldwide [27]–[29].

Further development of neurostimulator treatment of angina by directly manipulating the autonomic tone is not currently underway, as coronary revascularizations (percutaneous coronary intervention and bypass graft) and potent drugs have become the standard treatments of choice. Recently, however, spinal-cord stimulation used to relieve anginal pain in advanced ischemic heart disease has been reported to also improve some indexes of heart performance [30].

III. Treatment of Arrhythmias

Various forms of arrhythmia have been treated by stimulation of carotid sinus nerves and vagal nerves. Stimulation of carotid sinus nerves involves both the reflex-mediated inhibition of sympathetic nerves and activation of vagal nerves. Heidorn *et al.* [31] showed that massage of the carotid sinus in normal subjects changed the electrocardiogram and concluded that the carotid sinus baroreflex is a physiological phenomenon.

A. Carotid Sinus Nerve Stimulation

Carotid sinus massage was frequently used for bedside diagnosis and treatment of supraventricular tachyarrhythmias [32] in the era when diagnostic tools and antiarrhythmic drugs were limited. Later, Braunwald *et al.* [19] treated patients with supraventricular tachycardia by electrical carotid sinus nerve stimulation, using the same electronic device (Angistat, Medtronic) as used for the treatment of angina (see Section II for details). The authors concluded that electrical stimulation might reduce potential risks such as stroke associated with carotid sinus massage.

B. Vagal Nerve Stimulation

Direct electrical stimulation of the vagal nerve has once been abandoned due to frequent adverse effects. Vagal stimulation, however, has continued to attract the interest of cardiologists for the treatment of refractory arrhythmias including atrial fibrillation and/or life threatening arrhythmias (ventricular fibrillation). Mazgalev *et al.* [33]–[35] (Fig. 2) demonstrated in 18 dogs with simulated atrial fibrillation that electrical stimulation (Itrel II 7424, Medtronic; Photon ICD, St. Jude Medical) of the epicardial fat pad (at the junction of inferior vena cava and left atrium) was able to feedback-control the ventricular rate from 192 to 153 bpm at five weeks. The anatomical selectivity of vagal stimulation in targeting the atrioventricular conduction pathway suggested a minimum risk of adverse effects. In fact, the investigators continued this treatment for five weeks to six months in conscious dogs and reported no noticeable adverse

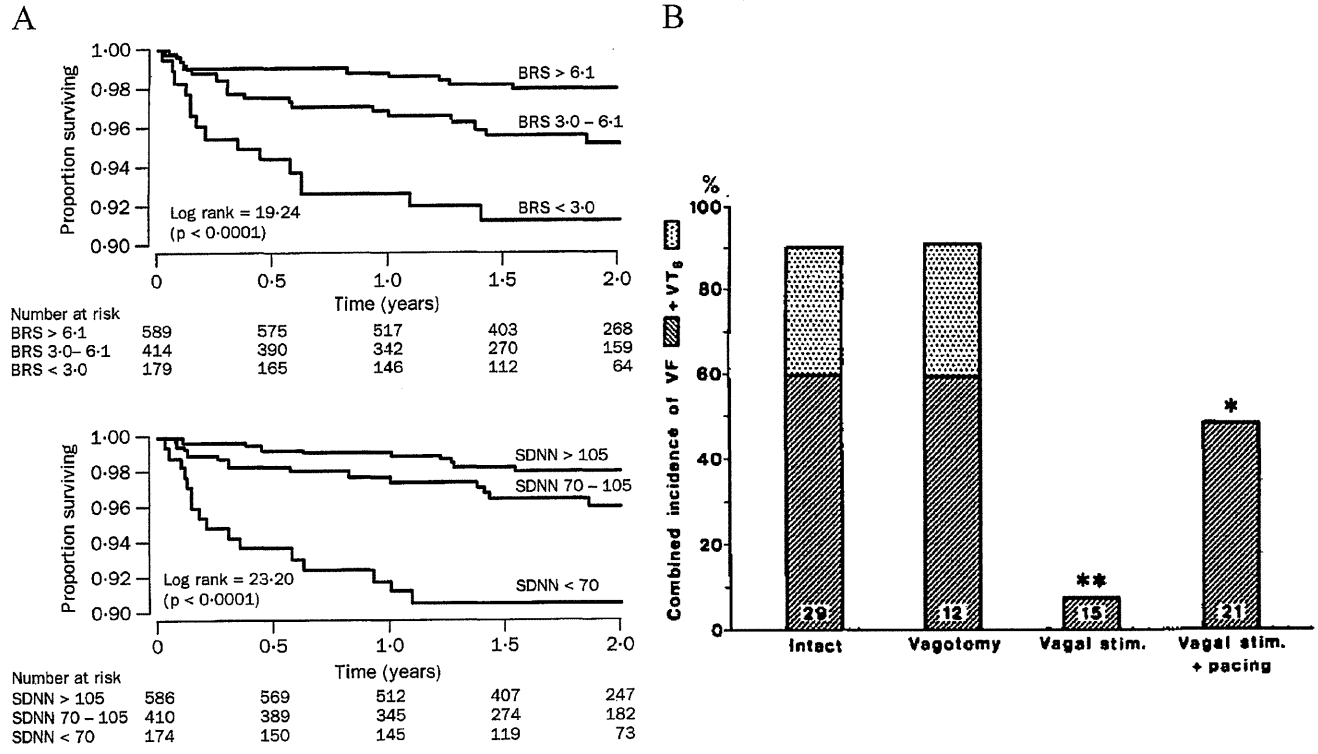

Fig. 3. (A) Survival (free from cardiac death or aborted cardiac arrest) in patients after myocardial infarction, plotted by baroreflex sensitivity (BRS) or by heart rate variability (SDNN). (B) Effect of efferent vagal stimulation (with vagotomy) started soon before reperfusion on incidence of Vf and sustained ventricular tachycardia (VTs) in cats with coronary occlusion and reperfusion. (*) $p < 0.005$ versus intact and $p < 0.05$ versus vagotomy. (**) $p < 0.001$ versus intact and vagotomy. (Reproduced from [43] (A) and [44] (B) with permission.)

effects [34]. They also proposed that the preservation of normal ventricular conduction pathway outweighed the hemodynamic effect of the loss of atrial contraction, as shown by comparing the rate control by fat pad stimulation and atrioventricular nodal ablation with right ventricular pacing [35], [36]. This finding is consistent with the equivalent outcomes of rate and rhythm control in recent large clinical trials [37]. Even in a patient with severe heart failure, short-term endocardial stimulation of fat pad has succeeded in rate control and eventual restoration from a decompensated state [38].

Vagal stimulation enhanced with choline esterase inhibitor, beta-adrenergic blocker, and/or calcium blocker has once been used to induce temporary asystole for surgical procedures [39]. Atrial vagal denervation (ablation) was attempted to prevent atrial fibrillation associated with excessive vagal activity but with limited success [40].

Using a clinically relevant disease model (healed anterior myocardial infarction superimposed with acute ischemia during exercise), Cerati and Schwartz [41] found that the residual vagal activity during ischemia protects against fatal ventricular fibrillation. The same group succeeded in quantifying the background vagal activity with baroreflex sensitivity index (increase in RR interval for a given increase in blood pressure). Higher pre- (>20 versus < 14 ms/mmHg) and postinfarction (>15 versus < 9 ms/mmHg) baroreflex sensitivity predicted resistance to ventricular fibrillation in dogs (risk of ventricular fibrillation, 35% versus 85%, and 20% versus 91%, respectively, both $p < 0.001$) [42]. In large clinical trials (ATRAMI), higher baroreflex sensitivity predicted better outcomes [43] [Fig. 3(A)]. The same group showed that electrical vagal stimulation even beginning just before reperfusion (i.e., at the end of ischemia) was protective against ventricular fibrillation during reperfusion [44] [Fig. 3(B)]. Ando *et al.* [45] proposed that vagal stimulation exerts anti-arrhythmogenic effects by preserving the functional connexin in intercellular junctions thereby maintaining synchronicity between myocardial cells.

C. *Neurally Regulated Artificial Pacemaker*

Artificial pacemakers are the ultimate solution for bradyarrhythmias. Although the pacemakers guarantee the rate of cardiac contractions, they are unable to reproduce native physiological rate regulation. Ikeda *et al.* [4] developed a pacemaker that reproduced physiological regulation of heart rate. They succeeded to decode the heart rate response from sympathetic nerve activity as the central message and found the decoding rule by a white-noise approach [4], [8], [9]. The root mean square error of heart rate control relative to the native heart rate was 1.4 to 6.6 bmp or $1.2 \pm 0.7\%$ of mean heart rate [4] (Fig. 1). The success of deciphering the central autonomic neural messages opens up new applications of regulating artificial organs directly by measuring the autonomic nervous activity. It allows the artificial organs to operate as if they are an integral part of the native system.

IV. Treatment of Hypertension

Hypertension is universally the most prevalent risk factor that aggravates atherosclerotic diseases. Despite numerous studies

over many years, the true cause of elevated blood pressure remains unsolved in most patients. Since lowering blood pressure delays the atherosclerotic process, numerous antihypertensive drugs have been developed and used clinically. Electronic treatment of hypertension was first developed for patients with severe drug-resistant hypertension at the time when fewer drugs were available. In recent years, however, the development of advanced neurostimulators as well as the recognition of a large population with drug-resistant hypertension have promoted the reappraisal of this device treatment.

A. Classical Neurostimulation

Hypertension has been treated electronically, almost exclusively by electrical stimulation of the carotid sinus nerve, which reflexly induces withdrawal of sympathetic nerve activity. Griffith *et al.* [46] investigated the effect of unilateral carotid sinus nerve stimulation in normal and renal hypertensive dogs. Except in hypertensive dogs with contralateral carotid sinus nerve sectioned, the hypotensive effect of carotid sinus nerve stimulation gradually decreased in 50 min. This attenuation may be partly due to the counteracting effect of remaining intact baroreflex components.

The first implantable carotid sinus neurostimulator was developed in the University of Minnesota by two surgeons [47]. This device delivered fixed-intensity stimulation synchronous to R wave to bilateral carotid sinus nerves. When evaluated in dogs, blood pressure was dramatically decreased in hypertensive dogs compared to normal dogs (systolic effect of 40–50 mm Hg versus 20 mmHg). Motivated by the study of direct carotid sinus nerve stimulation in man [48], Schwartz *et al.* [17] applied three types of baropacers (primary-celled, rechargeable, RF-coupled) to unilateral carotid sinus nerve in patients. In eight of 11 patients followed for five months to 2.5 years, the depressive effects persisted (systolic effect: 30–100 mmHg; diastolic effect: 24–80 mmHg). Agishi *et al.* [49] used mercury column as an on-off switch to automatically control pressure in dogs. Brest *et al.* [50] (eight patients) and Solti *et al.* [51] (one patient) described their experience of using a commercially available RF-coupled device (Barostat, Medtronic) for stimulating bilateral carotid sinus nerve. Using an externally worn transmitter, RF-coupled device allowed long-term treatment and external control of pulse amplitude and width. Electrical stimulation-induced hypotension was accompanied by bradycardia, a lower rate of pressure rise, lower cardiac index, and a decrease in vascular resistance relative to the level expected from significant hypotension.

Despite these earlier reports, device treatment of hypertension has almost disappeared until recently, due to the development of various classes of useful antihypertensive drugs. Moreover, in spite of reports of sustained hypotensive effect of carotid sinus nerve stimulation for over two years [50], arguments against the role of arterial baroreflex in chronic blood pressure regulation have gained widespread support. These arguments were based on the observation that blood pressure almost normalizes a few days after experimental sinoaortic denervation. This finding seemingly supports the notion of complete resetting of baroreflex and the role of the renin-angiotensin-aldosterone system in maintaining long-term blood pressure.

B. Role of Baroreflex Revisited in the Pathogenesis of Hypertension

Recently, using a carotid sinus nerve stimulation with neurostimulator (CVRx), Lohmeier *et al.* [52]–[57] showed that seven days of carotid sinus nerve stimulation induced sustained decrease in blood pressure associated with decrease in plasma norepinephrine but without increase in renin activity, suggesting a powerful role of baroreflex in chronic arterial pressure regulation [Fig. 4(A)]. The authors suggested that decreased renal sympathetic activity inhibits the increase in renin secretion during hypotension and enhances renal sodium secretion. The hypotensive effect did not persist in angiotensin-induced hypertension due to increased angiotensin level and when sympathetic tone and renin level were already suppressed before carotid sinus nerve stimulation [53] but did persist in obesity-induced hypertension [56]. Carotid sinus nerve stimulation decreased blood pressure to a greater extent than complete beta- and alpha1-adrenergic blockade, suggesting the pathophysiological relevance of postsynaptic alpha2-adrenergic mechanism [57]. Based on these results, the authors concluded that baroreflex is involved in chronic pressure regulation. Even though the resetting of baroreceptors cannot be denied, central resetting of baroreflex seems very small.

Another line of evidence also supports the role of baroreflex in chronic pressure regulation. Thrasher [58]–[64] has shown that chronic baroreceptor unloading (baroreceptor denervation except one carotid sinus, and ligation of common carotid artery of the remaining innervated carotid sinus) produces rather different pressor response than sinoaortic denervation. Chronic baroreceptor unloading maintained pressor response for at least seven days [58] [Fig. 4(B)], and although pressor response was reduced at five weeks, the magnitude was significantly greater than that of sinoaortic denervation [62] (decreased response may be due to increased sinus pressure by back pressure). He attributed the difference between chronic baroreceptor unloading and sinoaortic denervation to central adaptation in sinoaortic denervation. Reports by Munch *et al.* [65] on incomplete (56%) chronic resetting also supported a role of baroreflex in chronic pressure regulation. Taken together, there is no question that baroreflex plays a significant role in chronic blood pressure regulation. Hence a new model of carotid sinus neurostimulator (Rheos, CVRx), which is an external RF signal controllable, self-powered implantable device with long-life battery, would be a powerful clinical tool in controlling drug-resistant hypertension.

Unlike fixed-intensity carotid sinus nerve stimulation, development of sophisticated real-time feedback closed-loop neurostimulator requires control engineering. In an old article by Warner [66], the author failed to attenuate externally imposed cyclic pressure disturbances by a simple increase in baroreceptor gain. He correctly attributed this to the delay in pressure regulation. On the contrary, Kubota *et al.* [3] have shown that properly identified baroreceptor transduction in terms of transfer function reproduces similar level of pressure stability as native baroreflex.

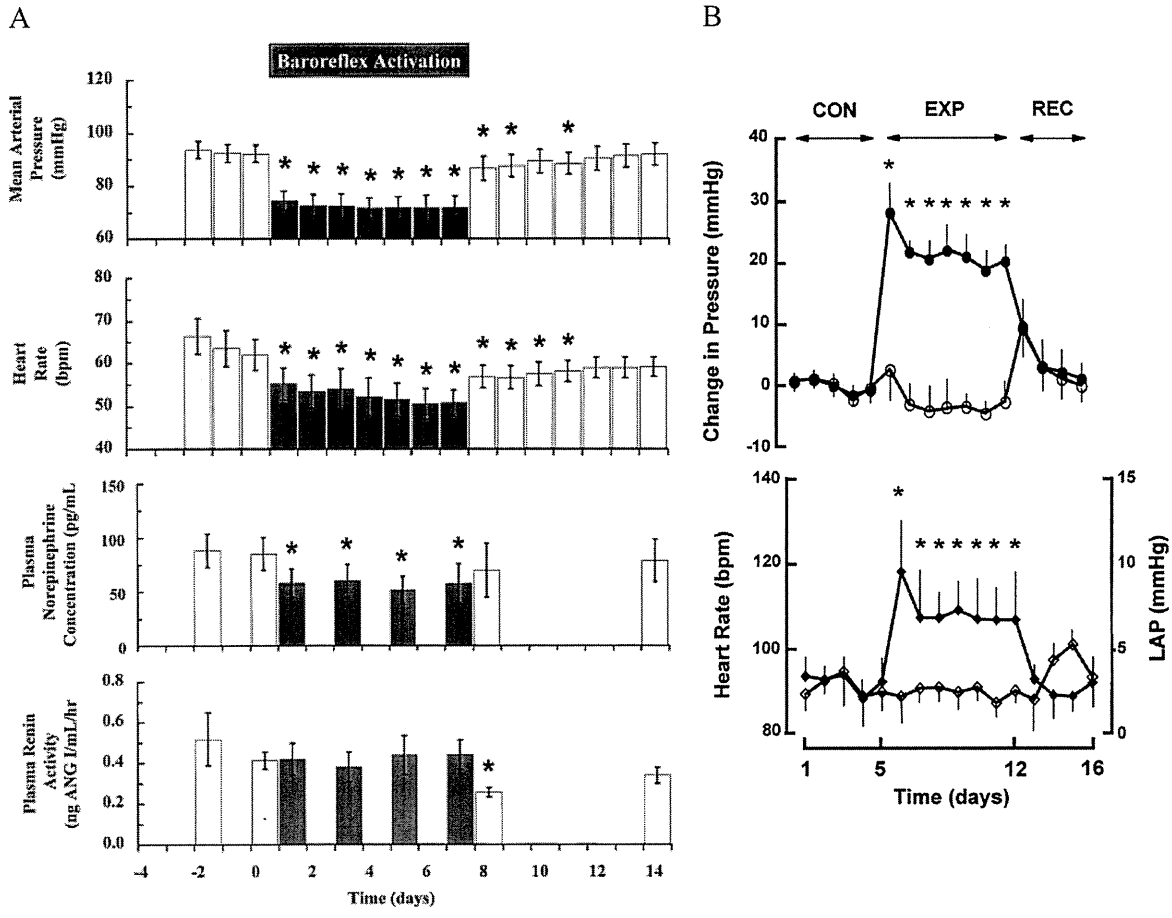

Fig. 4. (A) Effect of continuous baroreflex activation (bilateral carotid sinus stimulation) on mean arterial pressure, heart rate, plasma norepinephrine concentration, and plasma renin activity for seven days in six dogs. Due to decreased sympathetic activity, hypotension did not increase renin or decrease sodium excretion. (*) $p < 0.05$. (B) Chronic baroreceptor unloading (barodenervation and ligation of common carotid artery of the one remaining innervated carotid sinus) continuously increased blood pressure (closed circle) and heart rate (closed diamond) for seven days in dogs ($n = 5 \sim 6$). Open circle: carotid sinus pressure; open diamond: left atrial pressure (LAP). CON: control; EXP: baroreceptor unloading; REC: recovery; (*) $p < 0.05$. (Reproduced from [52] (A) and [58] (B) with permission.)

C. *Electroacupuncture*

Electrical acupuncture stimulation may be used to decrease blood pressure and decrease sympathetic nerve activity [67]–[70] [Fig. 5(A)]. Acupuncture stimulation changes the static properties of the central baroreflex controller in a direction of decreasing maximal sympathetic activity [67] [Fig. 5(A)] without changing the dynamic properties [68]. Kawada *et al.* [69] succeeded in developing a feedback depressor system by acupuncture in cats [Fig. 5(B)].

V. Treatment of Hypotension

Unlike hypertension, control of pressure against hypotension has been outside the scope of bionic cardiology. However, transient hypotension during, for example, postural change is one of the best targets for bionic cardiology for the following reasons. Severe orthostatic hypotension occurs as a result of damage to any of the components of the arterial baroreflex, including baroreceptors (neck surgery, radiation), vasomotor centers (Shy–Drager syndrome), and efferent pathways (spinal-cord injury). Hypotension is usually profound and requires prompt restoration with much shorter delay than is possible with any available drug to avoid syncope. Chronic pressor treatments should be avoided, as continuous hypertension increases the risk for atherosclerosis. For the above reasons, pharmacological treatments, either continued or on-demand, are obviously inappropriate. As patients may lose consciousness with sudden hypotension, fully automatic feedback control of pressure should be developed.

A. *Open-Loop Characterization of Baroreflex System*

To accomplish feedback pressure control, Sato *et al.* [10] and Kawada *et al.* [11] analyzed static open-loop characteristics of the two subsystems of the baroreflex: controller (discharging sympathetic nerve traffic in response to sensed pressure) and plant (changing pressure according to sympathetic nerve traffic). The actual operating pressure is determined by the intersection (i.e., equilibrium) between the two functional curves of subsystems. Sato *et al.* [12] and Ikeda *et al.* [13] analyzed the open-loop transfer functions over a wide frequency range. They demonstrated that the transfer function of the plant approximates a second order low-pass filter. In contrast, they demonstrated that the transfer function of the controller possesses derivative characteristic. By analyzing

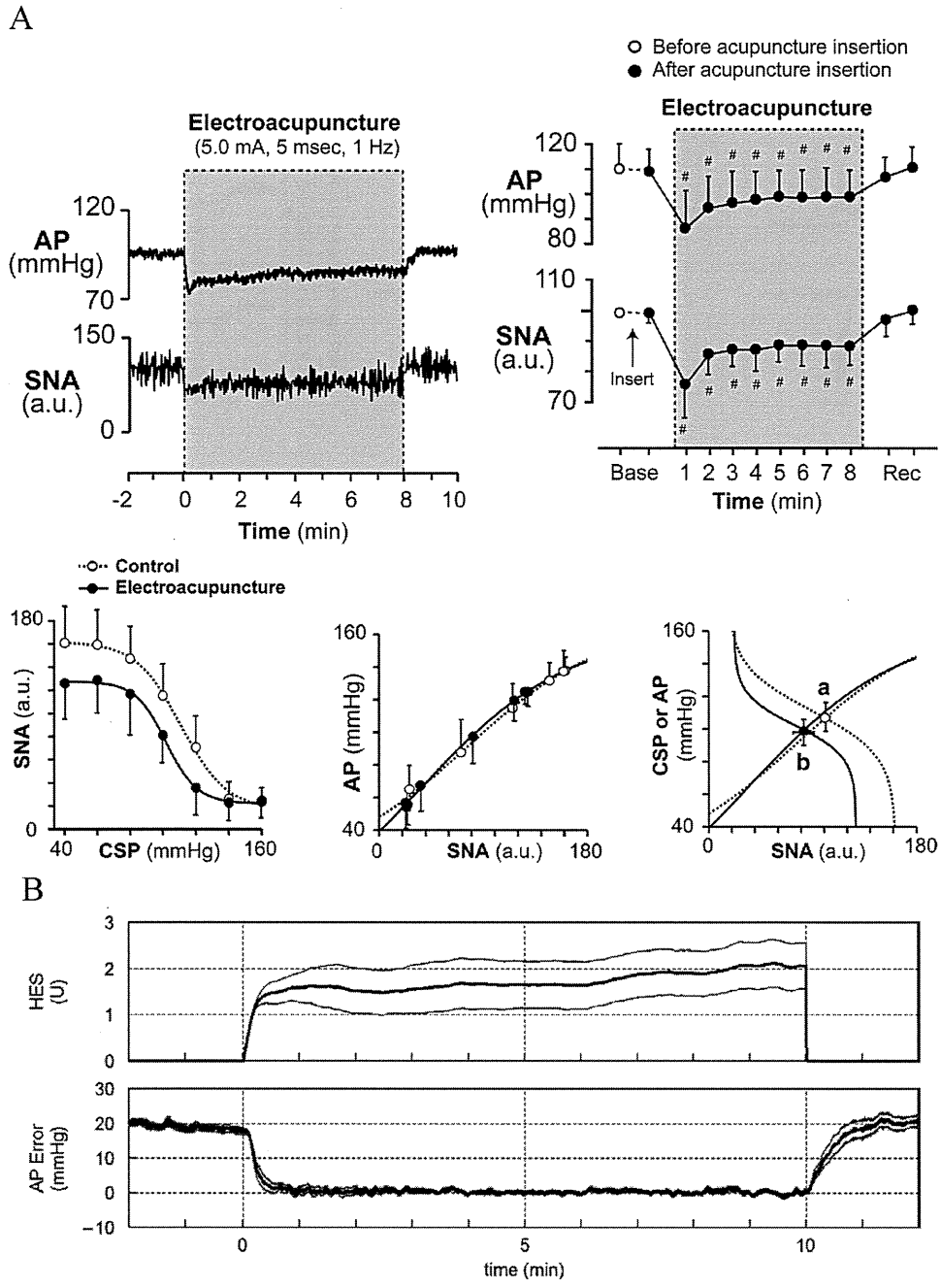

Fig. 5. (A) Electroacupuncture at Zusanli acupoint decreases arterial pressure (AP) and cardiac sympathetic nerve activity (SNA) for 8 min in six rabbits with intact baroreflex (top). Left: a representative example; right: pooled data (#) $p < 0.05$ versus baseline after acupuncture insertion. Hypotensive and sympathoinhibitory effect were due to the changes in controller (bottom left) but not plant (bottom center) of baroreflex. CSP: carotid sinus pressure. (B) Feedback control of AP by acupuncture-like hind-limb electrical stimulation (HES) in eight cats. Changes in HES is translated into changes in stimulus intensity (if HES > 1) and into changes in stimulus frequency (if HES < 1). (Reproduced from [67] (A) and [69] (B) with permission.)

these transfer functions, Ikeda *et al.* [13] have shown that the normal biological baroreflex is optimal to achieve quick and stable closed-loop responses.

B. Bionic Feedback Pressure Regulation

With the basic data at hand [14], Sato *et al.* [5], [6] designed a bionic baroreflex system by mimicking the functional biological baroreflex. The controller was designed so that the transfer function of the cascade of the controller and the biological plant (for stimulation of sympathetic celiac ganglion) matches that of the total-loop baroreflex. Therefore, the transfer function of the desired controller was obtained from the ratio of the transfer function of total-loop baroreflex to that of the plant. In ten rats depleted of functional baroreflex [6], the application of bionic baroreflex during a head-up tilt significantly ($p < 0.05$) attenuated blood pressure drop from 34 ± 6 to 21 ± 5 mmHg at 2 s, and from 52 ± 5 to 15 ± 6 mmHg at 10 s. The residual pressure drop was not different from that observed in rats with intact baroreflex [Fig. 6(A)].

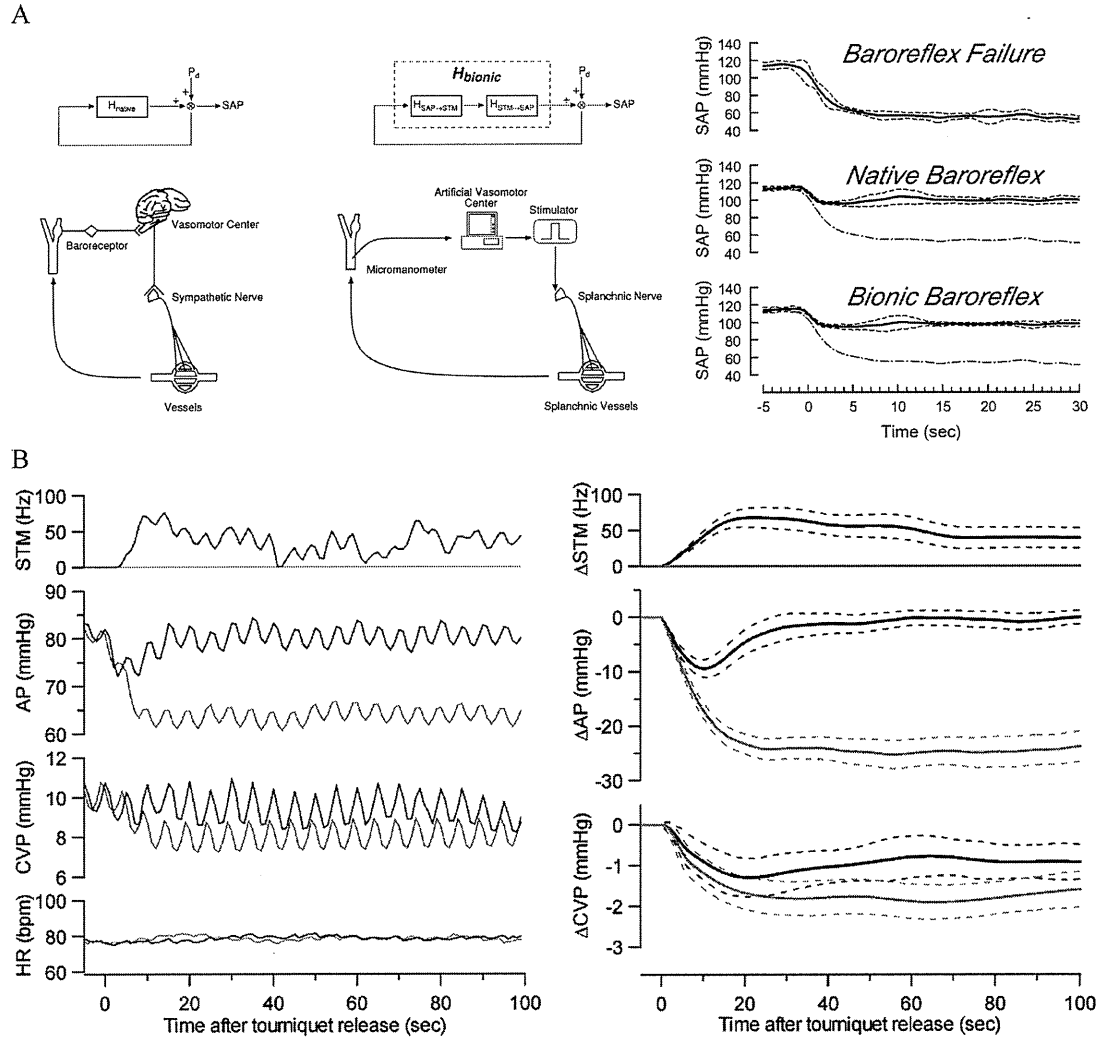

Fig. 6. (A) Functional and anatomical diagram of native baroreflex (left) and bionic baroreflex (center). Pd: pressure perturbation; SAP: systemic arterial pressure; H_{native}: open-loop transfer function of native baroreflex; H_{bionic}: open-loop transfer function of total bionic baroreflex; $H_{SAP \rightarrow STM}$: transfer function of designed bionic baroreflex controller; $H_{STM \rightarrow SAP}$: transfer function of native baroreflex plant. Changes in SAP in baroreflex failure, native baroreflex, and bionic baroreflex after head-up tilt (right). Dash-dot lines: average response in baroreflex failure. (B) Hypotension after tourniquet release was prevented by bionic baroreflex system using epidural spinal cord stimulation. Left: a representative patient; right: pooled data from 21 patients. STM: stimulation frequency; AP: arterial pressure; CVP: central venous pressure, HR: heart rate. (Reproduced from [5], [6] (A) and [72] (B) with permission.)

Yanagiya *et al.* [71] constructed a bionic baroreflex system using spinal cord stimulation via an epidural electrode catheter in six cats. They [71] designed the controller to provide quick and stable control only, rather than to mimic the biological controller. The system ameliorated a drop in pressure from 37 ± 5 to 21 ± 2 mmHg at 5 s and 59 ± 11 to 8 ± 4 mmHg at 30 s ($p < 0.05$). Epidural spinal-cord stimulation was further clinically applied by Yamasaki *et al.* [72] during surgery in a selected group of patients ($n = 12$) undergoing knee surgery. Pressure drop after tourniquet deflation was suppressed significantly ($p < 0.05$) from 17 ± 3 to 9 ± 2 mmHg at 10 s and 25 ± 2 to 1 ± 2 mmHg at 50 s [Fig. 6(B)]. Various inputs other than direct sympathetic stimulation may change blood pressure [67]–[70], [73]–[75]. Even noninvasive transcutaneous electrical stimulation [76] was developed for suppressing hypotension in patients with spinal-cord injury. In 12 patients, bionic feedback control restored the pressure drop by 50% in 35 ± 12 s and by 90% in 60 ± 18 s.

VI. Treatment of Heart Failure

A. Neurohormonal Activation Plays Major Roles in the Pathogenesis of Heart Failure

Heart failure is a complex syndrome that can result from any kind of cardiac diseases at their advanced stage. Mortality with this syndrome is considerably high even with the development of state-of-art treatments including artificial hearts, regenerative medicine, and cardiac transplantation. Recently, implantable device-based treatment of heart failure has attracted physicians' interest because of its enormous impact on survival. Available devices include implantable cardiac defibrillator to terminate fatal arrhythmia and cardiac resynchronization treatment device to improve the synchronicity of left ventricular contraction and hence cardiac performance. Device for bionic treatment of heart failure is now under aggressive development to complement the roles of these devices.

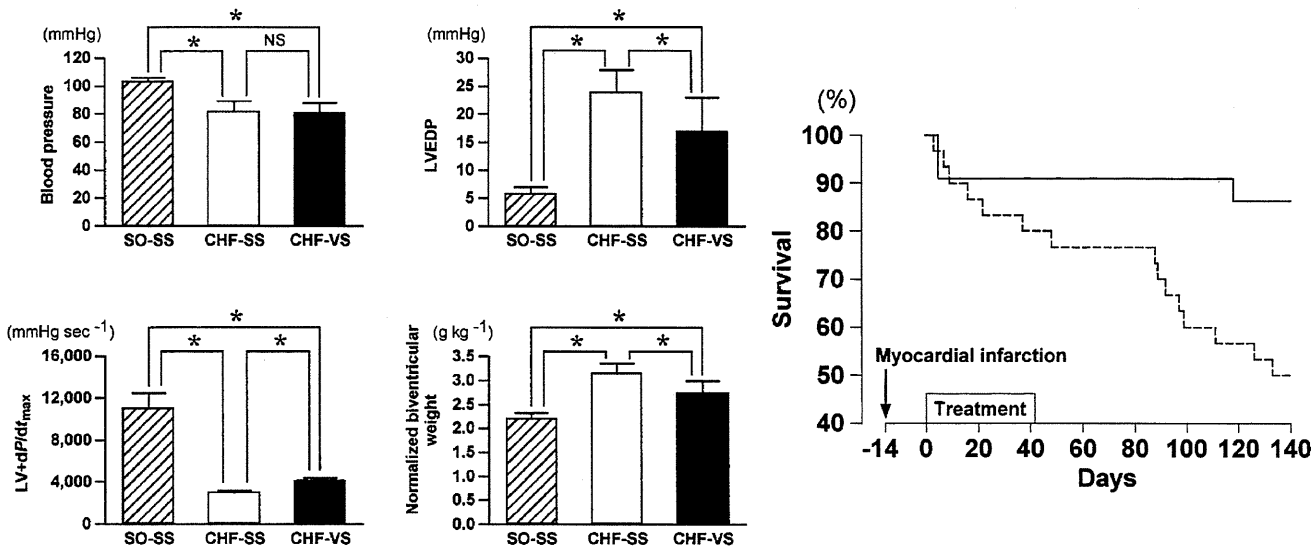

Fig. 7. Forty-two-day right vagal stimulation attenuated increased LVEDP, decreased maximal rate of left ventricular pressure rise (LV $+dP/dt_{max}$), increased normalized biventricular weight (left). SO-SS: sham-stimulated rats without failure (n = 9); CHF-SS: sham-stimulated rats with heart failure (n = 13); CHF-VS: vagal-stimulated rats with heart failure (n = 11); (*) $p < 0.05$. Survival for 140 days of rats with (solid line, n = 22) or without (dashed line, n = 30) 42-day vagal stimulation (right). (Reproduced from [78] with permission.)

Although the primary cause of heart failure is decreased pump function, the adjunct neurohumoral activation is certainly a major aggravating factor for disease progression and risk of death. Clinical trials on drugs for heart failure have revealed repeatedly that suppression of neurohumoral factors rather than increasing cardiac contractility improves survival. Pharmacological activation of vagal tone (such as low-dose scopolamine) [77] has been evaluated, but the effects on long-term survival have not been shown. With this background, bionic device therapy counteracting activated neurohumoral factors has been developed.

B. *Vagal Nerve Stimulation in Animal Studies*

Li *et al.* [78] first demonstrated that direct electrical stimulation of right vagal nerve (started after healing of extensive myocardial infarction) was effective in delaying the progression of heart failure and drastically improving survival in rats with heart failure. The intensity of vagal stimulation was low (decreasing heart rate by approximately 10%) enough to avoid adverse effects. They showed that vagal stimulation (control, n = 13; vagal stimulation, n = 11) significantly decreased left ventricular filling pressure from 24 ± 4 to 17 ± 6 mmHg, increased left ventricular $+dp/dt_{max}$ from 2987 ± 192 to 4152 ± 37 mmHg/s and decreased biventricular weight from 3.1 ± 0.2 to 2.8 ± 0.3 g/kg body weight, although the size of infarction was unchanged. Vagal nerve stimulation markedly improved survival from 50% to 82% ($p < 0.01$) at 140 days (Fig. 7). The same group also showed that vagal stimulation suppressed arrhythmias [79] and decreased both vasopressin secretion and salt ingestion [80]. The latter indicates the possible contribution of central modification induced by afferent nerve stimulation. Heart rate decreased progressively in six weeks. Vagal nerve stimulation protected the heart against acute ischemia, as well as reduced norepinephrine [81] and myoglobin [82] (an index of myocardial injury) release. These effects were attributed to its bradycardiac effect. Uemura *et al.* [83] investigated the effect of vagal nerve stimulation (−15 to 240 min) on matrix metalloproteinase (MMP) activity in a rabbit model of ischemia (60 min)-reperfusion (180 min) injury. Vagal stimulation increased the expression of tissue inhibitor of MMP-1 (TIMP-1) in cardiomyocytes and reduced active MMP-9. These molecular mechanisms of vagal stimulation might help prevent cardiac remodeling.

Some of the beneficial effects of vagal stimulation in heart failure may involve anti-inflammatory pathways. A large body of evidence [84]–[89] indicates that both afferent and efferent vagal nerves form anti-inflammatory pathways. The afferent vagal nerve senses local inflammation and transmits the information to the brain to suppress excessive inflammatory response in other areas in which inflammation may be elicited by the diffusion of various cytokines. In addition to recruiting the hypothalamic-pituitary-adrenal axis to release corticoids, the efferent vagal nerve is activated for faster anti-inflammatory response. The efferent activity stimulates nicotinic receptors on macrophages [84], and nicotinic alpha7 unit is essential for this regulation [86]. Activation of nicotinic receptors inhibits the release of pro-inflammatory cytokines such as TNF-alpha, IL-5, and IL-18 but does not inhibit the anti-inflammatory cytokine IL-10 [84]. Efferent vagal nerve stimulation is shown to decrease liver NF-kappa B, reduce plasma TNF-alpha, and revert hypotension in hemorrhagic shock (besides septic shock) through nicotinic receptors [89]. These findings indicate the involvement of inflammatory response in life-threatening cardiovascular disease such as hemorrhagic shock and heart failure.

C. *Vagal Nerve Stimulation in Patients With Heart Failure*

Recently, an implantable chronic vagal neurostimulator has entered clinical trial [90]. In this small-sized trial, the stimu-

lator (Cardiofit, BioControl) was implanted in 32 patients with heart failure (NYHA II to III, ejection fraction $\leq$ 35%). The right vagal nerve was stimulated intermittently (4 mA, 21% on). Heart rate decreased from 82 to 76 bpm; quality-of-life score (Minnesota Living with Heart Failure Questionnaire) improved from 48 to 32; 6-min walk increased from 410 to 471 m; and left ventricular ejection fraction increased from 23% to 27% in six months. The impact of vagal stimulation on the hard endpoint in these patients remains to be seen.

D. Carotid Sinus Nerve Stimulation in Heart Failure

Zucker *et al.* [91] examined if carotid sinus nerve stimulation (CVRx) improves the survival of dogs with pacing-induced (250 bpm) heart failure. They continued tachypacing until the endpoint (death or moribund state) was reached. Although the progression of heart failure (indicated by left ventricular end-diastolic pressure, left ventricular $+\mathrm{dp/dt_{max}}$, mean arterial pressure, heart rate, ejection fraction) was similar between dogs with and without carotid sinus nerve stimulation, increases in norepinephrine and angiotensin II were delayed in dogs with carotid sinus nerve stimulation. Dogs with carotid sinus nerve stimulation survived longer. How this observation translates to the clinical impact of carotid sinus nerve stimulation in patients with heart failure remains to be investigated.

VII. Autopilot Treatment of Acute Decompensated Heart Failure

Although neurohumoral suppression is the mainstay of long-term treatment for heart failure, a different strategy is required when the hemodynamics are acutely exacerbated. In order to save the lives of such patients, vital hemodynamic variables including blood pressure, cardiac output, and left atrial pressure have to be maintained within physiological ranges. Abnormality in each of these variables should be corrected promptly. The management of hemodynamic decompensation requires complex control of infusions of multiple potent drugs. The advent of automated feedback control of multiple drug infusions would have a major impact on clinical medicine. Such closed-loop feedback treatment involves control engineering and electronic controllers. This is also an important area of bionic cardiology.

A. Development of Integrative Cardiovascular Model

Various modalities of feedback control of hemodynamic variables using drug infusion have been attempted [92], [93], including those that control two variables. These attempts were only partially successful due to the complex interaction between variables. Results of these investigations prompted Uemura *et al.* [94], [97], [98] to take a different approach for hemodynamic control. They first established methods to break down each hemodynamic variable into fundamental physiological properties of the cardiovascular system. This was achieved by modeling the total cardiovascular system as the interaction of three different components: left heart pump, right heart pump, and total (systemic and pulmonary) vasculature [94], [96]. The model is an extension of Guyton's cardiovascular model [95] but differs from Guyton's model in several aspects: a third axis is incorporated to explicitly express left atrial pressure; the left and right heart pump functions are defined independently; and blood redistribution between systemic and pulmonary vasculature is expressed on the same venous return surface [Fig. 8(A)]. Using this model, Uemura *et al.* [94], [97] succeeded in delineating fundamental determinants of hemodynamics (left heart pump function, right heart pump function, systemic vascular resistance, and total stressed blood volume) from clinically measurable variables (blood pressure, cardiac output, left atrial pressure, and right atrial pressure).

B. Bionic Treatment of Decompensated Heart Failure

Based on their new model, Uemura *et al.* [98] designed a bionic controller that can simultaneously normalize blood pressure, cardiac output, and left atrial pressure accurately, quickly, and stably [Fig. 8(B)]. Their success is based on the effective decoupling of the complex interaction between variables, thereby allowing them to design three independent feedback control loops: left heart pump function controlled by an inotropic agent (dobutamine), systemic vascular resistance controlled by a vasodilator (sodium nitroprusside), and total stressed blood volume controlled by a volume expander and/or a diuretic (dextran solution, furosemide). Using the controller in 12 anesthetized dogs with severely decompensated heart failure restored the pump function, vascular resistance, and blood volume to normal levels in 30 min. As a result, blood pressure was controlled within 4.4 ± 2.6 mmHg, cardiac output within 5.4 ± 2.4 ml/min/Kg, and left atrial pressure within 0.8 ± 0.6 mmHg for another 30 min. The average amounts of drug use was dobutamine 4.7 ± 2.6 μg/min/kg, nitroprusside 4.2 ± 1.8 μg/min/kg, dextran infusion 2.4 ± 1.9 mL/kg, and furosemide 10 mg in one dog and 20 mg in another dog [Fig. 8(C)]. Even using the classical proportional-integral control for dobutamine and nitroprusside infusions and the "if-then" rule control for dextran/furosemide, control of multiple hemodynamic variables was possible and of good quality.

C. Beyond Hemodynamic Stabilization

Uemura *et al.* [99] attempted to further elaborate the treatment of decompensated heart failure beyond hemodynamic stabilization. They added myocardial oxygen consumption as an additional target for electronic control. The heart is an organ that consumes a large amount of oxygen and is highly vulnerable to oxygen shortage. Hayashida *et al.* [100] have shown in conscious dogs that the heart optimizes its metabolic efficiency during exercise as well as at rest. Theoretically, the optimal heart rate minimizes oxygen consumption for a given blood pressure, cardiac output, and left atrial pressure [101]. Uemura *et al.* [99] demonstrated in conscious dogs with acute decompensated heart failure that the automated electronic system of hemodynamic management allowed them to pharmacologically lower heart rate and myocardial oxygen consumption without compromising hemodynamics. The model-based approach to simultaneous optimization of multiple variables would help improve the outcome of patients with hemodynamic decompensation.

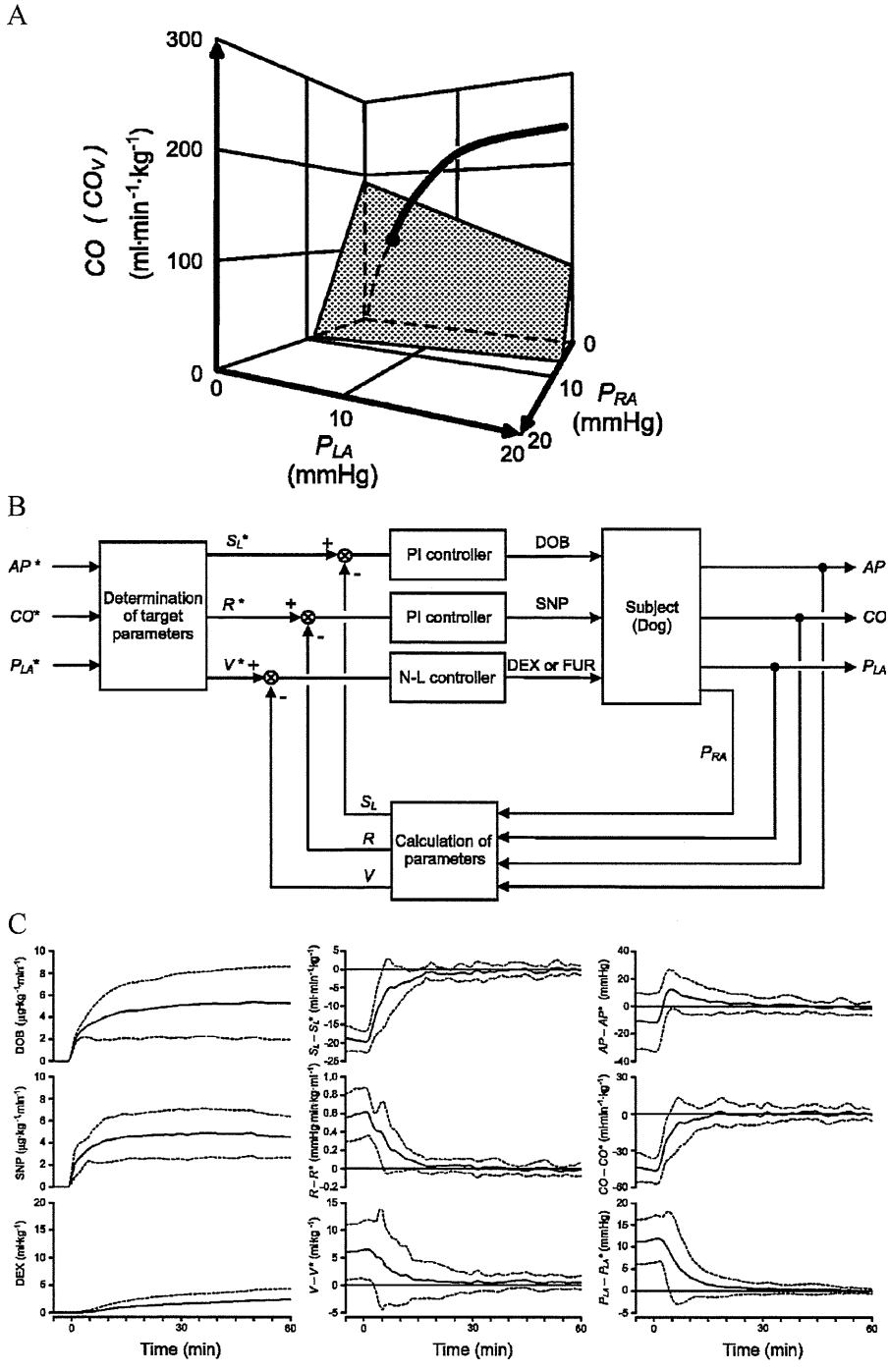

Fig. 8. (A) Extended Guyton's model of the total cardiovascular system. A third axis explicitly expresses left atrial pressure (P_{LA}), a cardiac output curve expresses left and right heart pump function independently, and a venous return surface expresses blood distribution in vasculatures. P_{RA}: right atrial pressure; CO: cardiac output; CO_V: venous return (= cardiac output). (B) Block diagram of an autopilot system for simultaneous control of systemic arterial pressure (AP), CO, and P_{LA}. Parameters with (*) indicate target values. From target variables, target values of left heart pump function (S_L), stressed blood volume (V), and systemic vascular resistance (R) are determined. S_L, V, and R of subjects are calculated from measured AP, CO, P_{LA}, and P_{RA}. Proportional-integral (PI) controllers adjust infusion rate of dobutamine (DOB) and sodium nitroprusside (SNP) to minimize the error in S_L and R, respectively. If-then rules adjust infusion of 10% dextran 40 (DEX) or injection of furosemide (FUR) to minimize the error in V. (C) Automatic correction of acute decompensated heart failure. Errors in cardiovascular properties (middle panels) (S_L, R, V) rapidly approached to zero, resulting in cardiovascular variables (right panels) (AP, CO, P_{LA}) approaching respective target. Left panels indicate infusion rate of DOB, SNP, and infused volume of DEX. (Reproduced from [98] with permission.)

VIII. Future of Bionic Medicine

We foresee a promising future for bionic medicine. It appears, however, that various factors may significantly influence the development and promotion of bionic cardiology. The first is the technology to interface native regulatory systems with bionic systems. The latest technology has made it possible to physically interface electronic devices with cardiac tissues (pacemaker, ICD). Neural interface, however, leaves much room for

improvement in terms of selectivity, stability, and durability. Sophistication of physical as well as logical neural interface will no doubt facilitate intricate body control. An advanced interface that allows stimulation at lower electrical power by minimizing current leakage and fully utilizing native excitation function will reduce adverse effects. Appropriate methods for the selective measurement and/or stimulation of subgroup of nerve fibers are necessary to match the spatial resolution indicated by the physiological/medical requirements. Autonomic function may be the first controllable function in the clinical setting compared to sensory or motor functions where intricate neural interface for higher spatial and temporal resolution is mandatory.

The second is the development of implantable long-term sensors. This factor would appear to be one of the basic needs, but has been relatively ignored until recently. For years, measurements have been limited to electrical signals. No durable sensors for mechanical or chemical variables are available. Once implanted, it is necessary to keep its accuracy even in blood for a considerably long term without repeated recalibrations. Therefore, the requirements of such sensors include long-term durability, stability, anticoagulation nature, and no need for recalibration.

The third is technology to support communication mechanisms in the body. Since the operation of bionic system is based on a closed feedback mechanism, various feedback loop components including sensors, controllers, actuators and plant have to communicate mutually. In the body, the neurohormonal mechanisms support this communication. In the bionic system, however, if some of these components are physically distant from each other, artificial communication mechanisms are needed for closed loop operation. We await the development of such an artificial communication mechanism in the body. The communication should simultaneous satisfy the short delay time (for real-time operation and closed-loop feedback), the sufficient bandwidth (depending on the application), the avoidance from interference from other communications and noises (guaranteeing secure feedback operation), and the mission-critical security (for medical need).

The fourth is the mechanism to support the power of bionic devices. This has been a significant problem, and will remain a target for research. The battery life should be long enough to be clinically meaningful. The size is preferable as small as possible. This is because the size of power supplies often determines that of the implantable devices. The third and fourth technology, if realized and combined, may obviate the use of leads, the most fragile part of implantable devices.

The fifth is the development of integrative science for biological system. To design elaborate feedback regulation of the cardiovascular system, in-depth knowledge of biological regulation is essential. Moreover, as already discussed in the Introduction, we have to go beyond the restoration of biological regulation to combat common diseases. Biological regulation has to be translated into and expressed in the "language" of control engineering. The expression should include dynamic, multiple-input, interactive, nonlinear, and feedback natures of the total system concerned. Besides these, we have to develop a model incorporating the effect of modifying biological regulation on the progression of common diseases. The development of such a model definitely requires biological research. Investigations of integrative biological regulation mandate the knowledge of both biology and engineering. It is our hope that many biomedical engineers will participate in the exploration into the development of bionic medicine.

The last factor is medical needs. Recent interest in device-based therapy will uncover the potential of bionic medicine in meeting the unmet needs. Of various cardiovascular diseases presented in this paper, the need for the appropriate treatment of chronic heart failure is most seriously unmet. Device-based therapy including bionic medicine is expected to complement existing treatment modalities to provide therapeutic benefits that cannot be achieved by drugs alone, especially for the increasing patients of chronic heart failure.

In conclusion, bionic medicine is the science to explore the wealth of controllable body parts. Bionic cardiology has a long history, through which we have accumulated much experience, generated knowledge on biological regulation, and identified unmet needs. These unique features together put us in a strong position to promote the development of more sophisticated device-based therapy for otherwise untreatable diseases. Bionic medicine will inspire more intricate applications in the twenty-first century.

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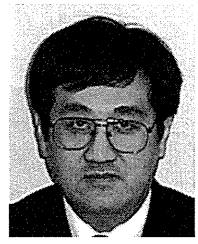

Masaru Sugimachi (A'98–M'06) received the M.D. degree and the Ph.D. degree in biomedical engineering from Kyushu University, Fukuoka, Japan, in 1984 and 1992, respectively.

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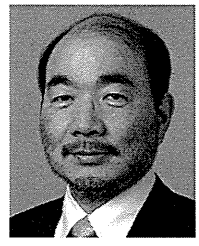

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Slow head-up tilt causes lower activation of muscle sympathetic nerve activity: loading speed dependence of orthostatic sympathetic activation in humans

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Kamiya A, Kawada T, Shimizu S, Iwase S, Sugimachi M, Mano T. Slow head-up tilt causes lower activation of muscle sympathetic nerve activity: loading speed dependence of orthostatic sympathetic activation in humans. *Am J Physiol Heart Circ Physiol* 297: H53–H58, 2009. First published May 15, 2009; doi:10.1152/ajpheart.00260.2009.—Many earlier human studies have reported that increasing the tilt angle of head-up tilt (HUT) results in greater muscle sympathetic nerve activity (MSNA) response, indicating the amplitude dependence of sympathetic activation in response to orthostatic stress. However, little is known about whether and how the inclining speed of HUT influences the MSNA response to HUT, independent of the magnitude of HUT. Twelve healthy subjects participated in passive 30° HUT tests at inclining speeds of 1° (control), 0.1° (slow), and 0.0167° (very slow) per second. We recorded MSNA (tibial nerve) by microneurography and assessed nonstationary time-dependent changes of R-R interval variability using a complex demodulation technique. MSNA averaged over every 10° tilt angle increased during inclination from 0° to 30°, with smaller increases in the slow and very slow tests than in the control test. Although a 3-min MSNA overshoot after reaching 30° HUT was observed in the control test, no overshoot was detected in the slow and very slow tests. In contrast with MSNA, increases in heart rate during the inclination and after reaching 30° were similar in these tests, probably because when compared with the control test, greater increases in plasma epinephrine counteracted smaller autonomic responses in the very slow test. These results indicate that slower HUT results in lower activation of MSNA, suggesting that HUT-induced sympathetic activation depends partially on the speed of inclination during HUT in humans.

autonomic nervous system; baroreflex; heart rate variability; microneurography

HUMANS HAVE BEEN SUBJECTED to ceaseless orthostatic stresses since they first evolved and assume an orthostatic posture most of their lives. Thus the maintenance of arterial pressure (AP) under orthostatic stress against gravity-driven fluid shift is of great importance. During standing, gravitational fluid shift toward the lower part of the body (i.e., abdominal vascular bed, lower limbs) would cause severe orthostatic hypotension if not counteracted by compensatory mechanisms (27). Orthostatic sympathetic activation mediated by arterial baroreflex has been considered to be the major compensatory mechanism (2, 26, 27) since denervation of baroreceptor afferents causes profound postural hypotension (30). Therefore, many earlier human studies have recorded muscle sympathetic nerve activity (MSNA) by microneurographic technique and investigated MSNA response to various orthostatic stresses such as head-up tilt (HUT) and lower body negative pressure (LBNP) (1, 5, 24). One of the important findings is that stronger orthostatic stress results in greater MSNA response during incremental HUT (3, 13, 14, 28) and LBNP (17), indicating the amplitude dependence of orthostatic MSNA activation. However, less attention has been paid to the effects of loading speed of orthostatic stress on orthostatic sympathetic activation in humans. Although earlier studies reported that rapid HUT causes dynamic and transient hemodynamic response (33, 34, 36), they did not investigate MSNA. Thus it remains unclear whether and how the inclining speed of HUT affects HUT-induced activation of MSNA (loading speed dependence of orthostatic MSNA activation), independent of the magnitude of HUT. This is an important clinical issue because the speed of upright tilting of each patient's bed would influence his/her autonomic nervous and hemodynamic conditions.

Orthostatic sympathetic activation is mainly mediated by arterial baroreflex control of MSNA, which exhibits high-pass filter dynamic transfer characteristics at least in anesthetized animals such as rabbits (15) and rats (29), indicating that more rapid change of AP results in greater response of MSNA to pressure change (15). Accordingly, we hypothesized that a lower speed of HUT results in less MSNA activation in humans. To test the hypothesis, we performed passive 30° HUT tests at three inclining speeds (1°, 0.1°, and 0.0167°/s) in 12 healthy volunteers. We compared the responses of MSNA measured by microneurography and hemodynamics during these tests.

METHODS

Subjects

The subjects were 12 healthy volunteers (10 males and 2 females) with a mean age (±SE) of 24 ± 5 yr, mean height of 164 ± 11 cm, and mean weight of 58 ± 9 kg. They were carefully screened by medical history, physical examination, complete blood count, blood chemistry analyses, electrocardiogram, and psychological testing. Candidates were excluded if they had evidence of cardiovascular or other disease, smoked tobacco products, took medications, or were obese (body mass index >30 kg/m^2). None of the subjects had experienced spontaneous syncope within the past 5 yr. All had a sedentary lifestyle and were not athletes. All subjects gave informed consent to participate in this study, which was approved by the

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Measurements

MSNA was measured in our laboratory by the method reported previously (22, 35). Briefly, a tungsten microelectrode (model 26-05-1; Federick Haer and Company, Bowdoinham, ME) was inserted percutaneously into the muscle nerve fascicles of the tibial nerve at the right popliteal fossa without anesthesia. Nerve signals were fed into a preamplifier (Kohno Instruments) with two active band-pass filters set between 500 and 5,000 Hz and were monitored with a loudspeaker. MSNA was identified according to the following discharge characteristics (22, 35): *1*) pulse-synchronous and spontaneous efferent discharges, *2*) afferent activity evoked by tapping of calf muscles but not in response to a gentle skin touch, and *3*) enhanced during phase II of the Valsalva maneuver.

AP was measured continuously using a finger photoplethysmograph (Finapres, Model 2300; Ohmeda, Englewood, CO) at the heart level. Systolic and diastolic AP was measured from the continuous pressure wave. Mean AP was calculated by averaging the pressure within a pulse wave. The finger pressure was confirmed to match intermittent (every minute) brachial AP measured by an automated sphygmomanometer (BP203MII; Nippon Colin, Komaki, Japan). In addition, distance between brachial cuff sensor and carotid sinus was measured in individuals, and AP at the height of carotid sinus level was then calculated by subtracting hydrostatic fluid pressure at each tilt angle from brachial AP. Electrocardiogram (chest lead II) and thermistor respirogram were also recorded continuously. A 20-gauge intravenous catheter was inserted into the antecubital vein in the left forearm to obtain venous blood samples for determination of plasma concentrations of epinephrine, norepinephrine, and arginine vasopressin. Thoracic impedance was measured using an impedance plethysmograph (AI-601G; Nihon Koden) to estimate tilt-induced decreases in thoracic fluid volume (12, 19).

Protocols

We instructed the subjects to refrain from eating for 3 h before the experiments. The experimental room was air-conditioned at a temperature of 26°C. Each subject was requested to remain supine on a tilt table set at 0° horizontally. After the microneurographic MSNA signal was detected and an intravenous catheter was placed, three HUT tests (control, slow, and very slow) were performed on each subject. The three tests were conducted in a random order, with intervals of at least 20 min between tests.

In the control test, the subject remained supine (0°) and rested for at least 20 min. Baseline blood sample was then collected, and baseline recordings of variables including MSNA were done for 10 min. Thereafter, the tilt table was inclined to 30° in a continuous passive manner at a speed of 1°/s. Thus inclination to 30° required 30 s. After reaching 30°, the tilt table was fixed for 8 min. All variables were monitored continuously. After that, a blood sample was again collected.

The slow and very slow tests were performed similarly to the control test except the speed of inclining the tilt table. The tilt table was continuously inclined to 30° at speeds of 0.1 and 0.0167°/s in the slow and very slow tests, respectively. Thus inclination to 30° required 300 s in the slow test and 1,800 s in the very slow test.

These HUT tests were terminated by returning the tilt table to the 0° horizontal position when any of the following incidents was observed: development of presyncope symptoms such as nausea, sweating, yawning, gray out, and dizziness; and progressive reduction in systolic blood pressure to <80 mmHg.

Data Analysis

Full-wave rectified MSNA signals were fed through a resistance-capacitance low-pass filter at a time constant of 0.1 s to obtain the mean voltage neurogram. The signals were then resampled at 200 Hz together with other cardiovascular variables. MSNA bursts were identified, and their areas were calculated using a computer program custom-built by our laboratory. MSNA was expressed as both the rate of integrated activity per minute (burst rate) and the total activity by integrating individual burst area per minute (total MSNA). Since the burst area, and hence also the total MSNA, was dependent on electrode position, they were expressed as arbitrary units (AU) normalized by the individual's baseline values at supine rest (0°) at the first HUT test (the average of total MSNA per minute during the 10 min of supine rest was given 100 AU). The area of each burst during the subsequent HUT tests was normalized to this value.

Time-dependent changes in amplitudes of low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.35 Hz) components of R-R interval variability were assessed continuously by complex demodulation using a custom-designed computer program (6, 8, 21). The complex demodulation technique is a nonlinear time-domain method of time series analysis suitable for the investigation of nonstationary/unstable oscillations within an assigned frequency band (8, 21). This method provides instantaneous amplitudes and frequencies of the LF and HF components as a function of time (8, 21). The instantaneous amplitude of HF component of R-R interval variability was used as the index of cardiac vagal nerve activity in this study.

Variables except blood data were averaged over every 10 min during 0° supine rest in all HUT tests. The data were averaged over every 10, 100, and 600 s during inclination of the tilt table from 0° to 30° in the control, slow, and very slow HUT tests, respectively, and averaged over every 1 min after reaching 60° HUT position in all HUT tests. In addition, the data were averaged over every 10° tilt angle during the inclining period.

Statistical Analysis

Data are expressed as means ± SE. Repeated-measure ANOVA was used to compare variables among the speed of HUT tests (control, slow, and very slow). When the main effect or interaction term was found to be significant, post hoc comparisons were made using the Sheffe's F procedure. A P value <0.05 was considered statistically significant.

RESULTS

Figure 1 shows the typical MSNA data during the control, slow, and very slow HUT tests in one subject. Although HUT increased MSNA during inclination of the tilt table from 0° to 30° in all three tests, the increase was apparently greater in the control test than in the slow and very slow tests (Fig. 1). Data from all subjects showed that increases in MSNA averaged over tilt angle (every 10° tilt) during inclination were greater in the control test than in the slow and very slow tests (Fig. 2). In the control test, MSNA showed a transient overshoot of 3 min after reaching 30° HUT and then declined gradually to the steady-state level (Fig. 2). In contrast, in the slow and very slow tests, MSNA reached steady-state levels without overshoot (Fig. 2). The steady-state levels were similar among the control, slow, and very slow tests.

Heart rate averaged over tilt angle (every 10° tilt) increased during all HUT tests, with similar increases in all three tests (Fig. 3). Instantaneous frequencies of LF and HF bands for R-R interval variability were 0.09 and 0.25–0.28 Hz, respectively, and were almost constant during all HUT tests. The LF amplitude of R-R interval variability did not change in any tests (Fig. 3). Of note, although the HF amplitude of R-R interval variability decreased during inclination of the tilt table from 0° to 30°, the decrease averaged over tilt angle was smaller in the

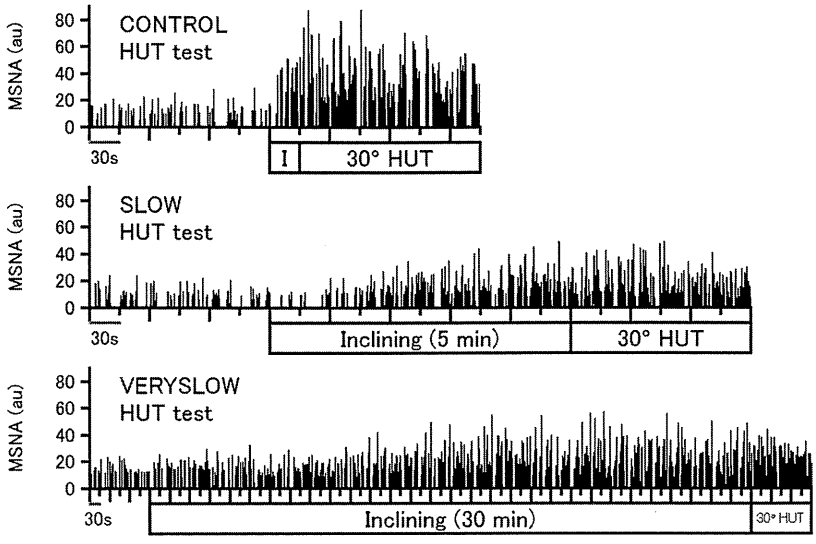

Fig. 1. Representative muscle sympathetic nerve activity (MSNA; integrated signals) data during control (*top*), slow (*middle*), and very slow (*bottom*) head-up tilt (HUT) tests in 1 subject. I (*top*), period of inclination of the tilt bed from 0° supine to 30° HUT posture at an inclining speed of 1°/s. Inclining (*middle* and *bottom*), period of inclination of the tilt bed at speeds of 0.1 and 0.0167°/s, respectively. au, Arbitrary units.

very slow test than in the control and slow tests (Fig. 3). Moreover, the HF amplitude of R-R interval variability reached steady-state levels after reaching 30° HUT, and the level was higher in the very slow test than in the control and slow tests (Fig. 3). Respiratory rate did not change in any tests (Fig. 3).

Systolic AP at the height of brachial level did not change, whereas diastolic AP at the level slightly increased during HUT in the control, slow, and very slow tests. However, there were no differences in both brachial systolic and diastolic APs among the control, slow, and very slow tests (Fig. 4). When AP at the height of carotid sinus level was predicted by subtracting hydrostatic fluid pressure at each tilt angle from brachial AP, systolic and diastolic AP at the carotid sinus level decreased during HUT similarly in the control, slow, and very slow tests (Fig. 4). Thoracic impedance increased during all HUT tests, and the changes averaged over tilt angle were almost identical in all three tests (Fig. 4).

When compared with the 0° supine level, plasma epinephrine concentration increased at the end of HUT tests, with greater increase in the very slow test (from 25.3 ± 3.7 to

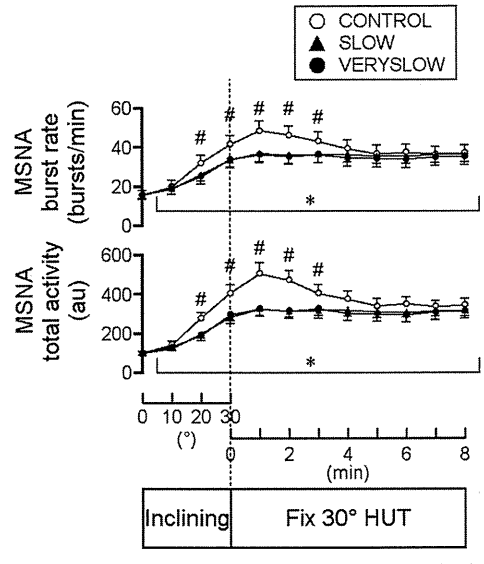

Fig. 2. MSNA burst rate and total activity during control (○), slow (▲), and very slow (●) HUT tests. The *x*-axis to the left of the vertical dotted line indicates that data are averaged over every 10° tilt angle during inclination from 0° supine to 30° HUT, and the *x*-axis to the right of the dotted line indicates that data are averaged over every 1 min after reaching 30° HUT. #$P < 0.05$ vs. slow and very slow tests; *$P < 0.05$ vs. 0° supine. Error bars denote SE.

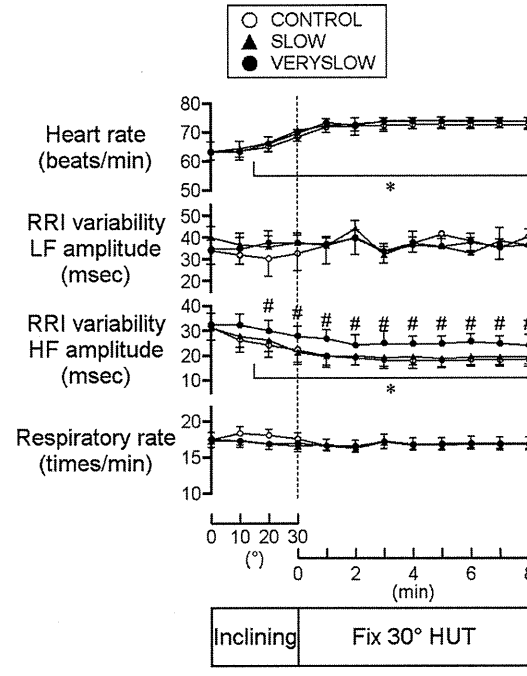

Fig. 3. Heart rate, amplitude of low frequency (LF) and high frequency (HF) component of R-R interval (RRI) variability, and respiratory rate during control (○), slow (▲), and very slow (●) HUT tests. The *x*-axis to the left of the vertical dotted line indicates that data are averaged over every 10° tilt angle during inclination from 0° supine to 30° HUT, and the *x*-axis to the right of the dotted line indicates that data are averaged over every 1 min after reaching 30° HUT. #$P < 0.05$ vs. control and slow tests; *$P < 0.05$ vs. 0° supine posture. Error bars denote SE.

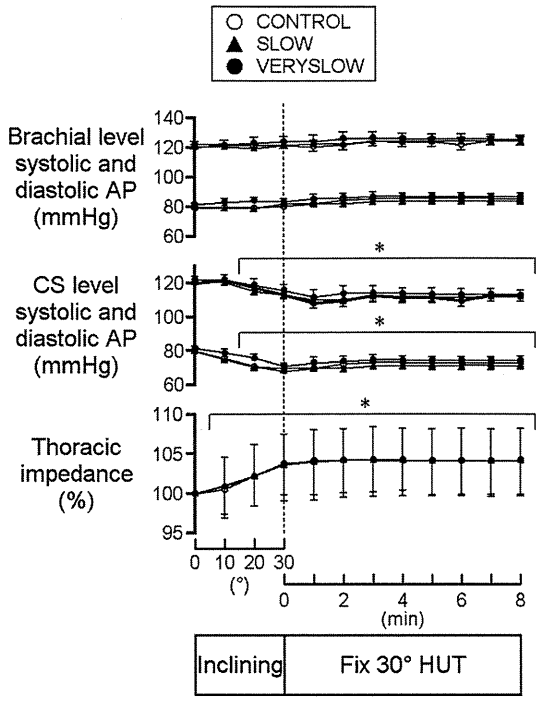

Fig. 4. Systolic and diastolic arterial pressure (AP) measured at the height of brachial level and predicted at the height of carotid sinus (CS) level, and thoracic impedance (percentage of baseline value at 0° supine) during control (○), slow (▲), and very slow (●) HUT tests. The *x*-axis to the left of the vertical dotted line indicates that data are averaged over every 10° tilt angle during inclination from 0° supine to 30° HUT, and the *x*-axis to the right of the dotted line indicates that data are averaged over every 1 min after reaching 30° HUT. *$P < 0.05$ vs. 0° supine posture. Error bars denote SE.

49.3 ± 7.4 pg/ml) than in the control (from 25.8 ± 4.0 to 35.1 ± 5.3 pg/ml) and slow (from 24.3 ± 3.5 to 36.0 ± 5.0 pg/ml) tests. Plasma norepinephrine concentration increased at the end of HUT tests similarly in the control (from 132.2 ± 10.4 to 180.2 ± 11.4 pg/ml), slow (from 134.0 ± 9.2 to 176.5 ± 9.8 pg/ml), and very slow (from 134.2 ± 10.7 to 179.4 ± 9.4 pg/ml) tests. Plasma arginine vasopressin concentration increased at the end of HUT tests similarly in the control (from 3.6 ± 0.4 to 3.9 ± 0.4 pg/ml), slow (from 3.6 ± 0.4 to 3.9 ± 0.4 pg/ml), and very slow (from 3.7 ± 0.4 to 4.0 ± 0.4 pg/ml) tests.

DISCUSSION

Speed Dependence of Orthostatic MSNA Activation

Many earlier human studies have reported that HUT at a larger tilt angle results in greater MSNA response, indicating the amplitude dependence of sympathetic activation in response to orthostatic stress. However, little is known about whether and how the inclining speed during HUT influences MSNA response to HUT, independent of the magnitude of HUT. Our major findings of the present study are that *1*) MSNA averaged over tilt angle increases during inclination of the tilt table from 0° to 30°, with smaller increase in the slow (0.1°/s) and very slow (0.0167°/s) tests than in the control tests (1°/s) and *2*) although a 3-min MSNA overshoot after reaching 30° HUT was observed in the control test, no overshoot was found in the slow and very slow tests. These results support our hypothesis that a lower speed of HUT results in less MSNA activation in humans, indicating the loading speed dependence of orthostatic MSNA activation. The speed-dependent sympathetic activation would contribute to prevent hypotension and maintain AP during rapid postural change from supine to upright posture.

Possible Mechanisms for the Speed Dependence of Orthostatic MSNA Activation

Since the HUT activates multiple physiological mechanisms, it is difficult to strictly determine the primary input to humans during postural change from the supine to upright postures. Therefore, we cannot conclude the true mechanisms for the speed dependence of orthostatic MSNA activation observed in this study. In this study, HUT decreased AP at the height of carotid sinus level decreased and increased thoracic impedance. We thus challenged to discuss possible relations of arterial and cardiopulmonary baroreflexes with the speed dependence of orthostatic MSNA activation.

Arterial baroreflex. Although arterial baroreflex is the major mechanism that increases sympathetic nerve activity (SNA) and maintains AP under orthostatic stress (2, 26, 27), it has high-pass filter dynamic transfer characteristics from baroreceptor pressure input to SNA. The high-pass filter characteristics have been investigated in detail by baroreflex open-loop experiments in anesthetized animals such as rabbits (11, 15) and rats (29). This indicates that more rapid change of AP resulted in greater response of SNA to pressure change. In addition, the high-pass filter characteristics might also be observed in earlier human study (10), since MSNA increased/decreased and turned to partially decrease/increase in response to stepwise neck pressure/suction. Although transfer function was not calculated in the study, the SNA response in humans may be consistent with the MSNA response (initial drop and partial recover) to stepwise increase in baroreceptor pressure in anesthetized animals (15) and suggests that the arterial baroreflex control of SNA in humans would also have the high-pass filter characteristics.

One possible mechanism for the lower MSNA during inclination in slower HUT tests is the high-pass filter characteristics of the arterial baroreflex control of SNA. Since the decreases in AP predicted at the height of carotid sinus level over tilt angle were similar in the control, slow, and very slow HUT tests, we assumed that the tilt-induced pressure perturbation was similar in the three HUT tests except for the speed. However, the high-pass filter characteristics of the arterial baroreflex control of SNA (11, 15, 16) would cause greater response of SNA to pressure change in the control HUT test that induced more rapid decreases in AP than the slow and very slow HUT tests. Of note, the dynamic transfer characteristics could not explain a few minutes of overshoot of MSNA activation after reaching 30° HUT posture observed in the control HUT test. Other mechanisms would be responsible for the overshoot of orthostatic MSNA response in faster HUT test.

Cardiopulmonary baroreflex. In addition to arterial baroreflex, cardiopulmonary baroreflex is known to mediate orthostatic activation of SNA. In our results, at a tilt angle of 10°, thoracic impedance increased similarly in control, slow, and very slow tests, indicating that the gravitational fluid shift directed toward the lower part of the body (such as the abdominal vascular bed and lower limbs) may be similar in all

three tests. In addition, MSNA increased at the tilt angle of 10° similarly in control, slow, and very slow tests, but AP predicted at the height of carotid sinus level did not change. These results suggest that cardiopulmonary baroreflex was activated by 10° HUT similarly in these tests and mediated similar magnitude of orthostatic MSNA activation but did not induce speed-dependent differentiation of MSNA. Therefore, it is possible that cardiopulmonary baroreflex control of MSNA does not have high-pass filter characteristics. However, since even small HUT can activate not only cardiopulmonary but also arterial baroreflexes similarly to low levels (i.e., −10 and −15 mmHg) of lower body negative pressure (4), it is difficult to isolate these baroreflexes and to conclude regarding the relation between cardiopulmonary baroreflex and the speed dependence of orthostatic MSNA activation in HUT. In addition, it was reported that cardiopulmonary and arterial baroreceptor afferents interact in a sense of a nonadditive attenuation (25).

Other mechanisms. Mechanisms other than baroreflexes might be responsible for the speed dependence of orthostatic MSNA activation. The first possibility is the vestibulosympathetic reflex, which may be involved in mediating pressor and sympathetic responses to orthostatic stress in rats (23) and humans (31). Since the reflex may be engaged differentially in the control versus the slow and very slow HUT tests, it can relate with the speed dependence of orthostatic MSNA activation observed in this study. The second possibility is the stroke volume, which had a close correlation with MSNA in their changes by orthostatic stress (20), although the neural pathway connecting stroke volume to MSNA may be unclear. Finally, humoral substances can relate with smaller activation of MSNA in the very slow HUT tests. In this study, increases in plasma epinephrine, not norepinephrine and arginine vasopressin, were greater in the very slow test than the control test.

Speed Independence of Orthostatic Tachycardia in the Present Study

In contrast with MSNA, orthostatic tachycardia is independent of inclining speed of HUT. The results may be consistent with a early study (32) that addressed more rapid HUT (i.e., 70° or 90° passive HUT in 3 s, and 70° passive HUT in 1.5 s) and reported that speed of HUT did not affect on initial heart rate responses to rapid HUT. It is difficult to understand the mechanisms for the finding. If baroreflex control of cardiac SNA is similar to that of MSNA as observed in rabbits (15), it is expected that the very slow test mediates a smaller increase in heart rate during inclination than the control test. This raises a possibility that mechanisms other than sympathetic control counteract the speed dependence of orthostatic sympathetic activation and result in speed-independent orthostatic tachycardia. Although we cannot measure cardiac vagal nerve activity in humans, there is a well-known, hypothetical consideration that the HF amplitude of R-R interval variability can reflect respiratory modulation of cardiac vagal nerve activity (7, 9). If so, our results suggest that the decrease in the index of cardiac vagal nerve activity averaged over tilt angle during inclination of HUT was smaller in the very slow HUT test than in the control test (indicating the speed dependence of orthostatic cardiac vagal suppression). Therefore, the speed independence of orthostatic tachycardia in the present study cannot be explained by autonomic neural controls. One possible explanation is that greater increase in plasma epinephrine counteracted the smaller response of sympathetic and, probably, vagal nerve activities.

Limitations

This study has several limitations. First, we used a mild to moderate HUT test (30°) in this study. Sequential HUT tests were necessary for this study, but sequential HUT tests at greater tilt angles (>60°) pose a problem in keeping constant electrode positions for microneurography and maintaining the quality of MSNA recording. Second, since we focused on the effects of slow-speed HUT on orthostatic MSNA response, we used inclining speeds of 1, 0.1, and 0.0167°/s in HUT tests. Finally, the HF amplitude of R-R interval variability is a limited measure of cardiac vagal control in the human (18), although we used it as an index of cardiac vagal modulation in the discussion.

In conclusion, although HUT at an inclining speed of 1°/s causes high MSNA activation with an overshoot of a few minutes, slower HUT (0.1 and 0.0167°/s) results in lower MSNA activation. This indicates that that HUT-induced sympathetic activation depends partially on the tilting speed in humans.

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