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Reduction of Myocardial Oxygen Demand by Controlling Heart Rate and Hemodynamics Simultaneously by Novel Circulatory Model

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***Abstract*—We were already capable of restoring automatically blood pressure, cardiac output, and left atrial pressure by an inotropic, a vasodilator, and volume infusion/a diuretic. Countermeasures for cardioprotection, however, should be integrated to improve the long-term outcomes. We established a full control of heart rate and examined if such a control was useful for decreasing cardiac oxygen consumption. Based on a simulation result, we conducted an animal experiment. In 7 dogs with acute heart failure, we treated hemodynamics, and then lowered heart rate. Compared to the treatment for hemodynamics alone, the addition of bradycardia decreased cardiac oxygen consumption. It was possible to maintain hemodynamics without sacrificing cardiac oxygen consumption.**

I. Introduction

THE ultimate goal of the treatment of acute failure is the restoration of failing hemodynamics. Although the native regulation for the cardiovascular system plays a role to sustain normal blood pressure when the severity of heart failure is mild (called compensated heart failure), the ability of native regulation is limited. To sustain life, not only blood pressure, but also peripheral perfusion (indexed by cardiac output) and the absence of pulmonary edema (indexed by low left atrial pressure) are necessary. The native regulation fails to restore cardiac output and left atrial pressure in advanced heart failure.

We have shown that with the use of an inotropic agent, a vasodilator, and volume infusion/a diuretic, we were able to restore automatically all of blood pressure, cardiac output, left atrial pressure [1]. In this study, the peripheral demand was fulfilled. The overload on the heart was, however, not ameliorated. Countermeasures for cardioprotection should probably also be a part of the treatment and should be integrated, so as to improve the long-term outcomes of the patient recovering from acute heart failure.

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We have already used the control of left ventricular contractility, systemic vascular resistance and blood volume to automatically restore blood pressure, cardiac output, and left atrial pressure. For the cardioprotection, we have to use the control of another cardiovascular property. We focused on the control of heart rate and examined if this was useful for the cardioprotection. We assumed here that low minute left ventricular oxygen consumption can be used as an index for cardioprotection.

II. Theoretical Analysis

A. Definition of the Problem

To supply the peripheral demand and to prevent pulmonary congestion, the cardiovascular system needs to operate with sufficiently high mean blood pressure (P_m), large cardiac output (CO), and low left atrial pressure (P_{LA}). Considering the physiologically normal values, we fixed P_m to 100 mmHg, CO to 100 ml·min^{-1}·kg^{-1}, and P_{LA} to 10 mmHg.

Even with these multiple constraints, the cardiovascular system does not operate with a unique condition. It can operate with various sets of contractility and heart rate (*see the next subsection B*). We simulated these various hemodynamics, and searched for the condition to minimize minute LV oxygen consumption [2].

B. Hemodynamics

We used left ventricular (LV) end-systolic pressure-volume relationship (ESPVR) and the framework of ventricular-arterial coupling to reproduce hemodynamics [3]. We approximated LV ESPVR by a straight line, and coupled end-systolic elastance (E_{es}) with effective arterial elastance (E_a). E_a was approximated by R/T, where R was systemic vascular resistance and T was heart period, reciprocal of heart rate (HR).

Using these approximations, for a given LV end-diastolic stressed volume (V_{eds}), stroke volume (SV) and CO can be calculated as

$$SV = V_{eds}\frac{T \cdot E_{es}}{T \cdot E_{es} + R} \quad (1)$$

$$CO = V_{eds}\frac{E_{es}}{T \cdot E_{es} + R} \quad (2).$$

LV end-systolic stressed volume (V_{ess}) and pressure (P_{es})

can be calculated as

$$V_{ess} = V_{eds} \frac{R}{T \cdot E_{es} + R} \quad (3)$$

$$P_{es} = V_{eds} \frac{E_{es} \cdot R}{T \cdot E_{es} + R} \quad (4).$$

In the framework of ventricular-arterial coupling, P_m was approximated by P_{es}. Systemic vascular resistance, R was therefore given by 1 mmHg·ml^{-1}·min·kg. Also, as P_{LA} was approximated by LV end-diastolic pressure (P_{ed}), V_{eds} would be calculated if we assume a predefined LV end-diastolic pressure-volume relationship (EDPVR). In this analysis, we used an exponential LV EDPVS as follows (V_{eds} in mL, P_{ed} in mmHg)

$$P_{ed} = \exp(0.082 \cdot V_{eds} - 0.8) + 2.03 \quad (5),$$

corresponding to the EDPVR with P_{ed} of 10 mmHg for V_{eds} of 35 ml.

Knowing R and V_{eds}, a necessary relationship between LV contractility (E_{es}) and heart period (T, an inverse of heart rate) is obtained. Even though it is necessary to follow this relationship to maintain P_m, CO, and P_{LA}, not a unique set of E_{es} and T would be obtained. Rather multiple sets of E_{es} and T would be feasible (*see the previous subsection A*).

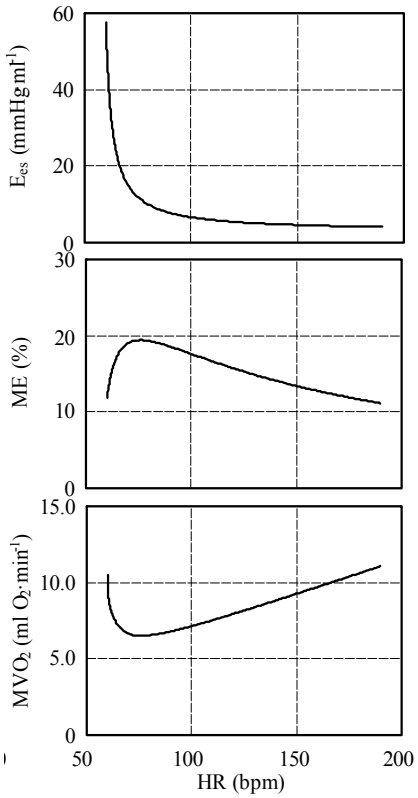

Fig. 1. Simulated relations of heart rate (HR) with left ventricular end-systolic elastance (E_{es}) (top), left ventricular mechanical efficiency (ME) (middle), and minute left ventricular oxygen consumption (MVO_2) (bottom), when mean blood pressure, cardiac output and left atrial pressure are kept at fixed values

C. Myocardial Oxygen Consumption

Beat LV oxygen consumption (BVO_2) was determined by PVA and E_{es} with high precision as follows [4]

$$BVO_2 = \alpha \cdot PVA + \beta \cdot E_{es} + \gamma \quad (6)$$

where α (1.8×10^{-5} mL O_2·mmHg^{-1}·mL^{-1}), β (1.8×10^{-3} mL O_2·mmHg^{-1}·mL), and γ (1.0×10^{-2} mL O_2) are constants. PVA stands for LV pressure-volume area (an index of total mechanical energy of LV contraction). PVA is the sum of LV stroke work (SW) and potential energy (PE). SW and PE are approximated as

$$SW = (P_m - P_{LA}) \cdot CO / HR \quad (7)$$

$$PE = P_{LA}^{\ 2} / 2E_{es} \quad (8).$$

Minute LV oxygen consumption per minute (MVO_2) and LV mechanical efficiency (ME) and are expressed as follows

$$MVO_2 = BVO_2 \cdot HR \quad (9)$$

$$ME = SW / BVO_2 = SW \cdot HR / MVO_2 \quad (10).$$

D. Simulation Results

Shown in Fig. 1 are simulation results. As explained in *subsection B*, there is an inverse relationship between E_{es} and heart rate [HR]. The top panel shows that if the heart is made bradycardiac, LV contractility should be enhanced to maintain P_m, CO, and P_{LA}, or to meet the peripheral demands.

The middle and the bottom panel show that ME would increase and MVO_2 would decrease by making heart bradycardiac up to a certain HR. Below this HR, however, rather ME would decrease and MVO_2 would increase with further decrease in HR. The differences in constants α, β and γ would change the optimal HR but would not change the basic relations show in Fig. 1.

E. Interpretation of the Simulation Results

As predicted by Eqs. 6 and 9, MVO_2 would largely be affected by HR. As MVO_2 is obtained by multiplying BVO_2 by HR, and as BVO_2 does not decrease much with HR, MVO_2 increases with HR.

In extreme bradycardiac condition, however, increase in E_{es} is so rapid, and the effect of increase in E_{es} overwhelmed the effect of HR.

ME is shown to be proportional to the reciprocal of MVO_2. Using, Eq. 7, the numerator of the right-hand side of Eq. 10, SW·HR is equal to $(P_m$-$P_{LA})$·CO and is constant.

III. Animal Experiment

We reproduced a similar condition as the previous simulation and examined if the same results would be obtained in an animal experiment [5].

A. Methods

We used 7 dogs for this animal experiment. These dogs were anesthetized and underwent coronary micro-embolization with glass beads. This procedure resulted in acute ischemic heart failure. We adjusted the size and the

dose of the emboli, so as to create heart failure severe enough that necessitated an intensive care. In these dogs, CO decreased by 39% (from 101±5 to 62±13 ml·min^{-1}·kg^{-1}), P_m decreased by 17 mmHg (from 114±4 to 97±14 mmHg), and P_{LA} increased by 8 mmHg (from 9 ± 1 to 17±2 mmHg).

To take the full control of HR in hand, a specific bradycardiac agent zatebradine (0.5 mg·kg^{-1}) was administered intravenously, and the intrinsic atrial beats were suppressed. Then, HR is fully controlled by atrial pacing. We first set HR at the rate before zatebradine infusion (146±8 bpm). In this condition (designated as *untreated*), we measured hemodynamics and cardiac energetics.

We then activated the autopilot system [1] we developed to maintain the desired P_m, CO, and P_{LA}. We customized in each animal the target values for P_m, CO, and P_{LA}. These ranged between 90 to 100 mmHg for P_m, 80 to 100 ml·min^{-1}·kg^{-1} for CO, and 10 to 12 mmHg for P_{LA}. The system restored P_m, CO and P_{LA} to their respective target values within 30 min. After confirming stable hemodynamics, (designated as *treated for hemodynamics*), we measured hemodynamics and cardiac energetics.

After the treatment of hemodynamics, we then reduced the atrial pacing rate in steps of 10 or 20 bpm. For each HR step, we waited until the hemodynamics stabilized. . We were able to reduce HR by 39±12 bpm. We measured hemodynamics and cardiac energetics at the lowest HR and stable hemodynamics (designated as *treated for hemodynamics and energetics*).

B. Results

We summarized the results of the animal experiment in Fig. 2. In each panel we plotted the pooled relationships between HR and various indexes of hemodynamics and cardiac energetics, in 7 dogs.

In *Untreated* condition (shown by open circles), CO was lower and P_{LA} was higher than normal. P_m was not so different from normal values. HR was quite high due to the activation of sympathetic nervous system.

By activating the autopilot system (*Treated for Hemodynamics* condition, shown by solid triangle), CO and P_{LA} were restored to the target normal values. P_m was slightly decreased. Because we are fully controlling HR, and we did not change the setting of HR, HR remained high also in this condition.

After decreasing HR to the lowest level (*Treated for Hemodynamics and Energetics* condition, shown by solid circle), all of CO, P_{LA}, and P_m remained the target normal values despite the large decrease in HR (CO: 89 ± 3 ml·min^{-1}·kg^{-1} to 88 ± 3 ml·min^{-1}·kg^{-1}, P_{LA}: 10.5 ± 0.4 mmHg to 10.9 ± 0.4 mmHg, P_m: 94 ± 3 mmHg to 93 ± 2 mmHg, all NS).

As shown in the right upper panel, the treatment for hemodynamics required the enhancement of contractility (E_{es}, $p<0.05$ vs. *Treated for Hemodynamics*); this is accomplished by the automatic infusion of a positive inotropic agent (dobutamine, increased from 1.4 ± 0.3 to 2.7 ± 0.5 μg·min^{-1}·kg^{-1}, $p<0.01$). With a decrease in heart rate, it is shown that a further increase in contractility was necessary to maintain CO, P_{LA}, and P_m. Doses for other drugs were also changed to maintain hemodynamics.

Although ME increased with the treatment for hemodynamics, this was at the expense of increasing MVO_2. With the treatment of hemodynamics and energetics, however, we were able to maintain hemodynamics, further improving ME ($p<0.01$ vs. *Treated for Hemodynamics*), and at the same time decreasing MVO_2 almost at the untreated level or rather to a lower level ($p<0.01$ vs. *Treated for Hemodynamics*). Even though we were unable to study extreme bradycardiac condition, a similar relationships were obtained as the theoretical analysis up to the heart rate studied (i.e., minimal heart rate was not below the optimal heart rate for minimizing myocardial oxygen consumption).

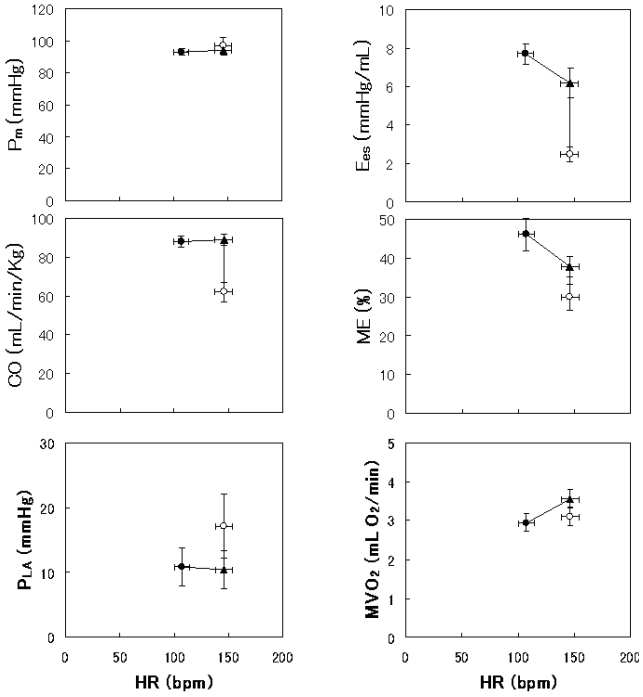

Fig. 2. Pooled relations between heart rate (HR) and mean blood pressure (P_m) (left top), cardiac output (CO) (left middle), left atrial pressure (P_{LA}) (left bottom), end-systolic elastance (E_{es}) (right top), left ventricular mechanical efficiency (ME) (right middle), and minute left ventricular oxygen consumption (MVO_2) (right bottom) in 7 dogs

IV. CONCLUSION

By taking full control of heart rate, and by adjusting treatment for hemodynamics at the same time, it was possible to maintain hemodynamics without sacrificing LV oxygen consumption.

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