Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Comprehensive Physiological Cardiovascular Model Enables Automatic Correction of Hemodynamics in Patients with Acute Life-Threatening Heart Failure

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Abstract—**Saving life of patients with acute life-threatening heart failure is a major challenge. One has to correct several fatal hemodynamic abnormalities at the same time within a limited time frame. The formulation of such complicated treatments enables the development of a system that can be used to save automatically lives of patients with acute heart failure, an autopilot system. To accomplish this, we established a comprehensive physiological cardiovascular model, on which we based the design of the autopilot system. By translating hemodynamics into cardiovascular parameters (pumping ability, vascular resistance, blood volume), and by controlling each of these with individual drugs, we were able to correct blood pressure, cardiac output, and left atrial pressure to the target values rapidly (5.2 ± 6.6, 6.8 ± 4.6, and 11.7 ± 9.8 minutes), stably, and simulataneously.**

I. Introduction

SAVING life of patients with acute life-threatening heart failure is a major challenge even for expert cardiologists. They have to correct several hemodynamic abnormalities, all of which make patients fatal, at the same time within a limited time frame before the patients deteriorate. The abnormalities include, at least, 1) decreased cardiac output (CO), 2) elevated left atrial pressure (LAP) (which disables oxygenation), and 3) hypotension or excessive hypertension.

There is a growing need to formulate such complicated treatments carried by limited numbers of expert cardiologists, so as practitioners or general physicians be able to reproduce the treatments and save lives, in the presence of increasing number of patients with severe heart failure. The formulation is useful not only for the education of general physicians, but also to develop a system that can be used to save automatically lives of patients with acute life-threatening heart failure.

Central to the development of formulated treatments is a comprehensive physiological cardiovascular model. The model was essential because we can ameliorate the difficulties in multi-input multi-output control system only by dissecting each physiological component and by selecting a corresponding drug to control this. Therefore, the aims of this study were to establish a comprehensive cardiovascular model, and to examine how rapidly and stably the automated feedback adjustments of drugs can correct three major hemodynamic abnormalities, i.e., CO, LAP, and blood pressure (BP) abnormalities.

Manuscript received April 3, 2006. This work was supported in part by Grant-in-Aid for Young Scientists (B) (16700379) from the Ministry of Education, Culture, Sports, Science and Technology, by Health and Labour Sciences Research Grants for Research on Medical Devices for Analyzing, Supporting and Substituting the Function of Human Body (H15-physi-001) from the Ministry of Health Labour and Welfare of Japan, and by the Program for Promotion of Fundamental Studies in Health Science of the National Institute of Biomedical Innovation.

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II. Model and Methods

A. Comprehensive Cardiovascular Model

We extended Guyton's circulatory equilibrium framework [1] to construct a comprehensive cardiovascular model. Guyton has modeled the whole circulation by dividing it into two components, cardiopulmonary component and systemic vascular bed. He characterized these parts by 'Cardiac output curve' and 'Venous return curve', respectively, and recoupled these curves. The intersection of these curves is the operating point of the circulation.

Guyton's model, however, was inappropriate for the use of the treatment of acute heart failure for the following reasons. First, the value of LAP is indispensable for the management of heart failure because higher LAP indicates pulmonary congestion and failure of oxygenation. One is unable to see LAP directly with Guyton's model. Second, in case of heart failure where only unilateral ventricle is damaged blood volume moves between pulmonary and systemic vascular beds. Such redistribution would shift venous return curve even though total blood volume is the same.

To circumvent these problems we developed a new cardiovascular model (Fig. 1) [2], [3]. We added a third axis of LAP, and expressed pumping ability of the both-sided heart as an integrated cardiac output (integration of CO-LAP relationship and CO-right atrial pressure [RAP] relationship) in three-dimensional space. Venous return curve was extended to a venous return surface, which shows that CO is

inversely related to both LAP and RAP. Blood redistribution would not change the surface as long as the total stressed blood volume is the same.

We have confirmed in dogs that venous return surface is linear and similar among animals, and that this model predicts hemodynamics after infusion or withdrawal of known amount of blood quite precisely (CO: y = 0.93x + 6.5, r^2 = 0.96, SEE = 7.5 ml·min^{-1}·kg^{-1}; LAP: y = 0.90x + 0.5, r^2= 0.93, SEE = 1.4 mmHg; RAP: y = 0.87x + 0.4, r^2= 0.91, SEE = 0.4 mmHg) [3].

Based on this model we parameterized the pumping ability of the left-sided heart (SL) as the ratio of CO to logarithm of LAP (SL=CO/[ln(LAP-2.03)+0.80]), systemic vascular resistance (R) as the ratio of BP-RAP to CO, and stressed total blood volume (V) as a linear function of CO, RAP, and LAP (V = (CO + 19.61RAP + 3.49LAP) ×0.129) (Fig. 2).

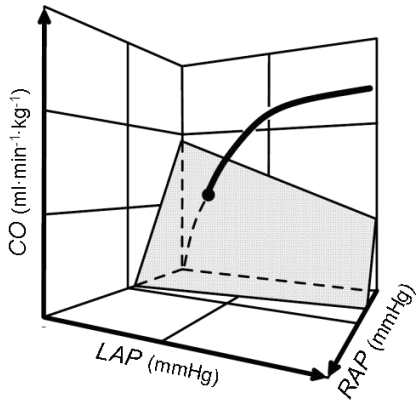

Fig. 1. Comprehensive cardiovascular model. The thick curve indicates the pumping ability of the left (CO-LAP relationship) and the right heart (CO-RAP relationship). The shaded surface characterizes the total (systemic + pulmonary) vascular beds; it remains constant as long as the total stressed blood volume is the same. CO, cardiac output; LAP, left atrial pressure; RAP, right atrial pressure.

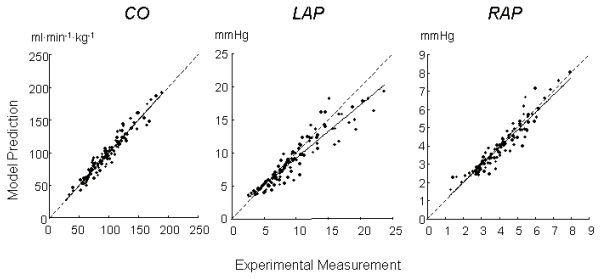

Fig. 2. Prediction of CO, LAP, and RAP based on extended Guyton's model.

B. Autopilot System

Fig. 3 depicts a block diagram of the autopilot system. S_L and R were controlled by proportional-integral (PI) negative feedback subsystems by adjusting infusion rates of dobutamine (DOB) and sodium nitroprusside (SNP), respectively. We infused 10% dextran 40 solution (DEX, 10 ml·min^{-1}) so long as V is less than target by >1 ml·kg^{-1}, and injected furosemide (FM, 10mg) every 20 minutes if V is larger than target by >2 ml·kg^{-1}.

Proportional (Kp) and integrative gain (Ki) values were calculated by Chien-Hrones-Reswick's method [4] from gain, time constant, and dead-time delay of the average approximated first-order step response (1) of S_L to DOB, and that of R to SNP.

$$\Delta S_L(t) = \begin{cases} G\{1-\exp[-(t-L)/T]\} & (t \ge L) \\ 0 & (t < L) \end{cases} \quad (1)$$

These step responses were obtained by infusing 6 mg·kg^{-1}·min^{-1} DOB for 10 min (10 dogs), and by infusing 2 mg·kg^{-1}·min^{-1} SNP for 10 min (6 dogs).

C. Animal Experiments

We evaluated the performance of autopilot system in 12 adult anesthetized mongrel dogs (both sexes, 25±4 kg). BP was measured with a pressure transducer (DX-200, Nihon Kohden) and a fluid-filled catheter (8Fr) placed in the right femoral artery. CO was measured with an ultrasonic flow meter (20A594, Transonics) placed around the aortic root through a median sternotomy and a small pericardial incision. LAP and right atrial pressure were monitored continuously with the same transducers and fluid-filled catheters placed in left and right atria, respectively. The junction between the vena cavae and the right atrium was taken as the zero-pressure reference.

We inserted a catheter (6Fr) in the right femoral vein to infuse DEX with a computer-controlled roller pump (Minipuls 3, Gilson). A second double-lumen catheter was introduced into the right femoral vein for administration of DOB and SNP with respective computer-controlled infusion pumps (CFV-3200, Nihon Kohden). FM was given through a jugular venous catheter manually according to the computer commands.

These dogs were then subjected to left ventricular failure by coronary microembolization until LAP reaches > 18 mmHg or CO decreases < 70 ml·min^{-1}·kg^{-1}. After hemodynamics became stable, we applied the autopilot system. We set target S_L, R, and V so as these parameters

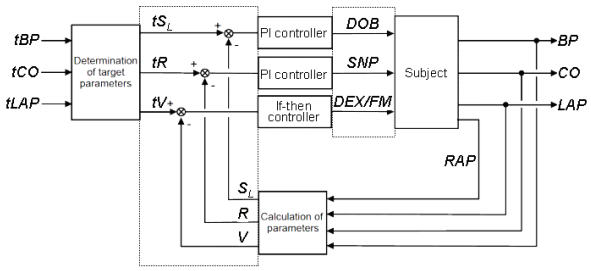

Fig. 3. Block diagram of autopilot system. Hemodynamic variables were translated into parameters characterizing pump function, vascular resistance, and blood volume, and these parameters were individually controlled by changing dose of drugs most suited to change each parameter preferentially. Target parameter values were determined based on target hemodynamics.

result in the predefined target BP (between 90-105 mmHg), CO (90-100 ml·min^{-1}·kg^{-1}) and LAP (8-12 mmHg) values. We observed the performance of the system over 50-60 min.

III. Results

Based on the average step response, we determined the PI gain for SL control as Ki = 0.01 sec-1, Kp = 0.06 mg·kg^{-1}·min^{-1} (ml·min^{-1}·kg^{-1})$^{-1}$ and that for R control as Ki = 0.007 sec^{-1}, Kp = -1.37 mg·kg^{-1}·min^{-1} (mmHg·min·ml^{-1}·kg)$^{-1}$.

Fig. 4 shows an example of the autopilot. Soon after the system was activated at 0 min, infusion rates of DOB, SNP, and DEX were continuously controlled so that S_L, R and V reach their respective target values. The rapid, sufficient and stable control of these parameters resulted in the rapid, sufficient and stable control of hemodynamics, i.e., BP, CO and LAP in 30 minutes.

In 12 dogs, with DOB (4.7 ± 2.6 mg·kg^{-1}·min^{-1}), SNP (4.2 ± 1.8 mg·kg^{-1}·min^{-1}), DEX (2.4 ± 1.9 ml·kg^{-1}), and FM (10 mg in one, 20 mg in one), BP, CO, and LAP rapidly converged to the target values in 5.2 ± 6.6, 6.8 ± 4.6, and 11.7 ± 9.8 minutes, respectively. These values remained stable after they reached the target (RMS values for BP=4.4 ± 2.6 mmHg, CO=5.4 ± 2.4 ml·min^{-1}·kg^{-1}, LAP=0.8 ± 0.6 mmHg)

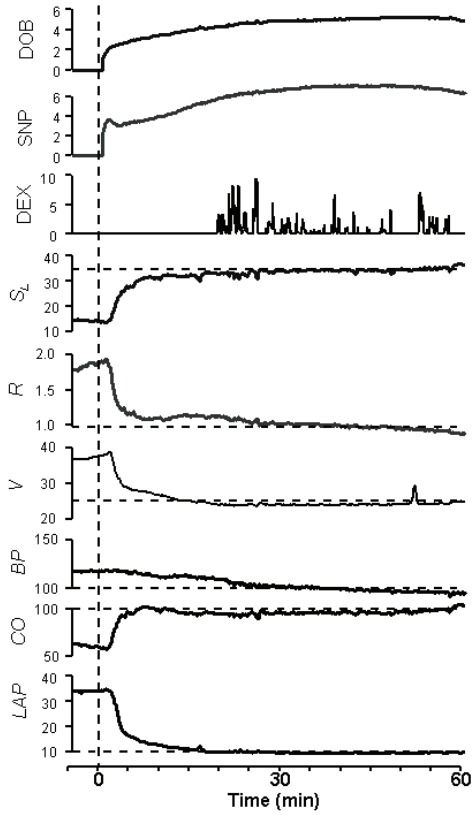

Fig. 4. An example of the correction of hemodynamics with the autopilot system. By normalizing pump function (S_L), resistance (R), and blood volume (V) with the administration of dobutamine (DOB), sodium nitroprusside (SNP), and dextran 40 solution (DEX), respetively, all of the abnormal hemodynamics (increased blood pressure [BP], decreased cardiac output [CO], and elevated left atrial pressure [LAP]) resolved rapidly, sufficiently, and stably.

IV. Discussion

We have shown that by translating hemodynamic variables into cardiovascular parameters (pumping ability, vascular resistance, and blood volume), and by controlling each of these parameters with individual drugs with preferential effect on the parameter, we were able to correct automatically major hemodynamic abnormalities rapidly, stably, and simultaneously.

Our approach to control cardiovascular parameters rather than to control hemodynamic variables has a couple of advantages. First, these parameters are directly related to mechanical properties of heart and vasculatures. Second, these parameters are likely to behave more independently than hemodynamic variables. For example, enhanced contractility increases both BP and CO.

Third, our approach is also advantageous from the perspective of control engineering. Because we selected drugs that have a preferential effect on one of the parameters, the complex multi-input multi-output system can be effectively decoupled into three single-input single-output subsystems. This is why we only need four input (dose of drug)-output (change in parameter) relationships, i.e, namely, DOB-S_L, SNP-R, DEX-V, and FM-V relationships. Although we found various non-preferential effects (DOB decreases R and increases V; SNP increases SL and decreases V), these non-preferential effects were not large enough to induce significant interactions among the three closed loops This also permits system operators to understand its behavior easily.

Although we fixed the PI gain constants and "if-then" rules, controls of cardiovascular parameters are accurate and stable. There are inter- and intra-individual differences in the response of the parameters to drug infusion. However, our results indicate that the three drug controllers effectively compensate for all of these differences, and do not require adaptive tuning in individual animals as in the previous system.

Our system explicitly quantifies cardiac pump function, vascular resistance (afterload), and blood volume (preload), thereby controlling the overall hemodynamics. We believe that this unique feature of our system is intuitively appealing, is important for education, and is acceptable to clinicians. We believe that formulation of treatments will be extended to other diseases in the near future.

V. Conclusion

By controlling cardiovascular parameters such as pump function, vascular resistance, and blood volume, the autopilot system allows simultaneous control of BP, CO, and LAP with reasonable accuracy and stability, and is potentially a powerful clinical tool for the management of patients with

acute life-threatening heart failure.

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