Automated drug delivery system to control systemic arterial pressure, cardiac output, and left heart filling pressure in acute decompensated heart failure

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Abstract: We have developed a novel automated drug delivery system for simultaneous control of systemic arterial pressure (AP), cardiac output (CO), and left atrial pressure (PLA) in acute heart failure. The circulatory equilibrium framework we established previously discloses that AP, CO, and PLA are determined by equilibrium of the mechanical properties of the circulation, i.e. pumping ability of the left heart, stressed blood volume and systemic arterial resistance. Our system directly controls the three mechanical properties with cardiovascular drugs including inotropes and vasodilators, thereby controlling AP, CO, and PLA. In heart failure dogs, our system, once activated, quickly restored normal values of AP, CO, and PLA with sufficient accuracy and stability, which indicates the validity of our approach.

Key words: computers, heart failure, drugs, negative feedback, hemodynamics

1. INTRODUCTION

In the management of patients with acute heart failure after myocardial infarction or following cardiac surgery, cardiovascular agents such as inotropes and/or vasodilators are commonly used to control systemic arterial pressure (AP), cardiac output (CO) and left atrial pressure (PLA). Since responses to these agents vary between patients and within patient over time, strict monitoring of patient condition and frequent adjustments of drug infusion rates are usually required. This is a difficult and time-consuming process, especially in hemodynamically unstable patients.

Although several closed-loop systems [1, 2] to automate drug infusion have been developed to facilitate this process, no closed-loop system so far developed is capable of controlling the overall hemodynamics; i.e., controlling AP, CO and PLA simultaneously. This is because all previous systems attempted to directly control AP and CO by estimating response of the variable to drug infusion [1, 2]. This approach is inapplicable because of the difficulties to estimate simultaneous AP, CO and PLA responses to the infusion of multiple drugs.

In this study, we developed a new automated drug delivery system to control AP, CO and PLA [3, 4]. To overcome the difficulty of the previous systems, our system adopted an original approach. We previously developed a circulatory equilibrium framework by extending the Guyton’s classic framework [5]. As shown in Figure 1, the extended

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Fig. 1. Diagram of circulatory equilibrium for CO, venous return (COv), PLA, and PRA. The equilibrium CO, PLA and PRA are obtained as the intersection point of the venous return surface and integrated cardiac output curve.
framework consists of an integrated cardiac output curve characterizing the pumping ability of the left and the right heart, and a venous return surface characterizing the venous return property of the systemic and pulmonary circulation [6-8]. The intersection point of the integrated CO curve and the venous return surface predicts the equilibrium point of CO, PLA and right atrial pressure (PRA) (Fig. 1). Once CO, PLA and PRA are predicted from the intersection point, systemic arterial resistance determines AP. Based on this framework, instead of directly controlling AP, CO, and PLA, our system controls the integrated CO curve with dobutamine (DOB), the venous return surface with 10% dextran 40 (DEX) and furosemide (FUR), and systemic arterial resistance with sodium nitroprusside (SNP), thereby controlling AP, CO and PLA. The purpose of this study was, therefore, to develop and validate the automated drug delivery system.

2. METHODS

2.1 Automated drug delivery system

The integrated CO curve is parameterized by the pumping ability of the left heart (SL) [ml·min⁻¹·kg⁻¹], the venous return surface by total stressed blood volume (V) [ml·kg⁻¹], and the systemic arterial resistance by R [mmHg·ml⁻¹·min·kg⁻¹] which are calculated for a given set of AP, CO, PLA and PRA as the following formulas [3, 4];

\[ S_L = \frac{CO}{\ln(P_{LA} - 2.03) + 0.8} \]  
\[ V = (CO + 19.61P_{RA} + 3.49P_{LA}) \times 0.129 \]  
\[ R = (AP - P_{RA})/CO \]

Fig. 2. Schematic illustration of an automated drug delivery system for simultaneous control of AP, CO and PLA. Proportional-integral (PI) feedback controllers adjust infusion rate of DOB and SNP to minimize the difference between target and subject’s SL and those of R, respectively. Nonlinear (N-L) feedback controller adjusts infusion of DEX or injection of FUR to minimize the difference between target and subject’s V.

Figure 2 is a schematic illustration of the automated drug delivery system [3, 4]. Once target values for AP, CO and PLA are defined and fed into the computer, it calculates the target values for SL, R, and V using Equations (1)-(3). The subject’s SL, R, and V are calculated from measured AP, CO and PLA values using Equations (1)-(3). To minimize the differences between target and subject’s SL and R, proportional-integral feedback controllers adjust the infusion rates of DOB and SNP, respectively. To minimize the difference between target and subject’s V, a nonlinear feedback controller adjusts the infusion of DEX or injection of FUR. Gain and rules of the controllers were predefined on the basis of the step responses of SL, R, and V to the infusions of the drugs [3, 4]. The adjustment processes are repeated in parallel and continued until the differences disappear.

2.2 Animal experiments to validate performance of the automated drug delivery system

In 12 anesthetized dogs, we acutely created ischemic heart failure by coronary embolization, which decreased CO from 133 ± 42 to 69 ± 22 ml·min⁻¹·kg⁻¹, AP from 109 ± 18 to 91 ± 17 mmHg and increased PLA from 7 ± 2 to 19 ± 6 mmHg. We connected the animals to the system, and defined target AP (90-105 mmHg), target CO (90-100 ml·min⁻¹·kg⁻¹) and target PLA (8-12 mmHg), which were fed into the system to determine target values for SL, R, and V as described above. The controllers were then activated by closing the loops. We observed the performance of the system over 50-60 min.
3. RESULTS

Figure 3 shows the experimental trial in a representative animal. The system was activated at 0 min. Figure 3A shows the time courses of the infusion rates of DOB and SNP, and the accumulated volume of infused DEX. In this case, FUR was not injected. Figure 3B shows the time courses of SL, R and V. Infusion rates of DOB, SNP, and DEX were adjusted so that SL, R and V reached their respective target values. By controlling the cardiovascular parameters, the automated system controlled AP, CO and PLA accurately and stably as demonstrated in Figure 3C. AP, CO and PLA reached their respective target levels within 30 min and remained at these levels [3].

In 12 animals, the average times for AP, CO and PLA to reach the acceptable ranges (+/−10 mmHg of target AP, +/−10 ml·min⁻¹·kg⁻¹ of target CO, +/−2 mmHg of target PLA) were 5.2 ± 6.6 min, 6.8 ± 4.6 min, and 11.7 ± 9.8 min, respectively. The average standard deviations from the target values were small for AP [4.4 ± 2.6 mmHg], CO [5.4 ± 2.4 ml·min⁻¹·kg⁻¹] and PLA [0.8 ± 0.6 mmHg] [3].

4. DISCUSSION

Our system controls the mechanical determinants of circulation, and as a result achieves target values for hemodynamic variables [3, 4]. Previous systems attempted to control hemodynamic variables by estimating the apparent input–output relations between drug infusion and response of the controlled variables. In the systems that control AP and CO, all possible input–output relations have to be estimated; namely, inotrope–AP, inotrope–CO, vasodilator–AP, and vasodilator–CO relations [2]. The reason is that these drugs affect AP and CO simultaneously to almost the same degree. If this previous approach is applied to simultaneous control of AP, CO and PLA, at least 9 input–output relations have to be estimated, since at least 3 drugs are required to independently control the three variables. This would make the system extremely complicated, and therefore be practically unfeasible. The three drug controllers in our system (Figure 2) are designed on the basis of only three input–output relations between drug infusion and response of the controlled parameter; namely, DOB–SL, SNP–R and DEX/FUR–V. The fact that the three closed loops are effectively decoupled simplifies the entire system. This also permits a system operator, who would be a physician, untrained in control engineering, to understand its behavior easily.

5. CONCLUSION

By directly controlling the mechanical properties of the heart and vessel, our automated system enables comprehensive management of hemodynamics in acute heart failure.

6. REFERENCES


