Less invasive approach to automated closed-loop control of hemodynamics in decompensated heart failure

Kazunori UEMURA, Toru KAWADA, Can ZHENG and Masaru SUGIMACHI
Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center

Abstract: We have been developing a computer-controlled infusion system of cardiovascular drugs (vasodilator, inotropes, diuretics, volume-expander) to automatically optimize arterial pressure (AP), cardiac output (CO), and pulmonary wedge pressure (PCWP) in heart failure (HF). In our previous developments, however, CO and PCWP were measured through thoracotomy, and inotropes were inevitably infused, which were clinically impractical or not in line with HF guidelines. We have made the system less invasive and clinically feasible. CO and PCWP were estimated and monitored less-invasively utilizing transthoracic-echocardiography. Control algorithm was revised in accordance with the guidelines. We applied the system to 9 HF dogs. Once activated, our system immediately started infusions of vasodilator/diuretics in all animals. Inotropes was not used in 3, and used at minimal doses in 6 animals that were intolerant of vasodilators. Hemodynamic variables were controlled to their targets accurately. In conclusion, the advanced system may be useful in managing patients with HF.

Keywords: Hemodynamics, heart failure, closed-loop control, cardiovascular drugs.

1. Introduction

We have been developing a computer-controlled infusion system of cardiovascular drugs (vasodilator, inotropes, diuretics, volume-expander) to automatically optimize arterial pressure (AP), cardiac output (CO), and pulmonary wedge pressure (PCWP) in decompensated heart failure (HF). Based on a framework of circulatory equilibrium, our system estimates systemic arterial resistance (R), total stressed blood volume (V) and Frank-Starling slope of the left ventricle (S) from AP, CO, and PCWP. In canine models of decompensated HF, our system successfully controlled AP, CO, and PCWP with good accuracy and stability, which suggests the potential clinical utility of the system. However, our prototype system had two drawbacks. First, CO and PCWP were measured invasively through thoracotomy, which was impractical in clinical settings. Second, inotropes were inevitably infused, which was not in line with HF guidelines, which recommend to treat decompensated HF initially with vasodilators and diuretics to improve congestion. Use of inotropes is strictly limited to those who have symptomatic hypotension despite adequate filling pressure, or are intolerant of intravenous vasodilators.

The purpose of this study was to make the system less invasive and clinically feasible.

2. Design of Automated Cardiovascular Drug Infusion System

Figure 1 is a schematic illustration of the automated cardiovascular drug infusion system developed in this study. CO and PCWP are estimated and monitored continuously using minimally invasive monitors that we have developed recently. Our CO monitor automatically determines peak velocity of the ascending aorta using continuous-wave Doppler transthoracic echocardiography, and cardiac ejection time and aortic cross sectional area using the pulse contour of the radial arterial pressure. These signals are continuously processed to estimate CO (COest). PCWP (PCWPest) was estimated from jugular venous pressure (JVP) corrected by the ratio of tissue-Doppler peak systolic velocity of tricuspid annulus (Ss) to...
that of mitral annulus (S\textsubscript{m}) (JVP·S\textsubscript{T}/S\textsubscript{m}).\textsuperscript{9}

To minimize the use of the inotropes, we designed new control logic in accordance with the following concept.\textsuperscript{7} S is related to R, left ventricular (LV) end-systolic elastance (E\textsubscript{es}, an index of LV contractility), heart rate (HR) and diastolic myocardial stiffness (κ) as follows\textsuperscript{2}

\[ S = \frac{E_{es}}{\kappa / (E_{es} / HR + R)} \] (1)

Inotropes improve S by improving E\textsubscript{es}. Eq. (1) also indicates that reduction of R using vasodilators increases S for given E\textsubscript{es} and HR. However, extreme reduction of R may decrease AP to an unacceptable range. Hence, it is possible to improve S using vasodilators (without using inotropes) as long as AP is maintained within an acceptable range. Otherwise, inotropes should be used to improve S and prevent hypotension.

User inputs an acceptable lower limit value for AP (aAP), and target values for CO (CO\textsuperscript{*}) and PCWP (PCWP\textsuperscript{*}), from which target values of AP (AP\textsuperscript{*}), R (R\textsuperscript{*}), V (V\textsuperscript{*}), and S (S\textsuperscript{*}) are determined. Proportional-integral (PI) feedback controllers adjust infusion rates of a vasodilator, sodium nitroprusside (NP) and an inotrope, dobutamine (DOB) to control R and S, respectively. Nonlinear (N-L) feedback controller adjusts injection of a diuretic, furosemide (FUR) or infusion of a volume-expander, 10% dextran 40 (DEX) to control V. As long as AP\textsuperscript{*} is not lower than aAP, the feedback loop of DOB infusion ($) is left open. If AP\textsuperscript{*} is less than aAP, AP\textsuperscript{*} is reset to aAP, and $ is closed to control S by DOB, not by NP.

3. Methods and Results of Experimental Validation

We used 9 adult mongrel dogs. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). All protocols were approved by the Animal Subjects Committee of the National Cerebral and Cardiovascular Center.

In the dogs, we created HF by chronic (3 weeks) right ventricular tachycardia pacing, which decreased LV ejection fraction significantly from 59 ± 12 % to 23 ± 7 % (P < 0.01).

We then connected the system to HF dogs under general anesthesia, and activated the system (Figure 2). Our system immediately started NP and FUR, and if necessary started DEX/DOB, and optimized R, V and S in 30 minutes.\textsuperscript{7} DOB was not used in 3, and started and used at minimal doses in 6 animals that were intolerant of vasodilators. Normalization of R, V and S resulted in restoring normal AP, CO\textsubscript{est} and PCWP\textsubscript{est} with small deviations from targets values (Figure 2). Pulmonary artery catheterization confirmed optimization of hemodynamics (AP, from 98±4 to 74±11 mmHg; CO, from 2.2±0.5 to 2.9±0.3 L·min\textsuperscript{-1}·m\textsuperscript{-2}; PCWP, from 27.0±6.6 to 13.8±3.0 mmHg).\textsuperscript{7}

4. Conclusions

To the best of our knowledge, this is the first report of an automated cardiovascular drug infusion system that successful optimized overall hemodynamics in HF subjects using minimally invasive monitors while conforming to clinical guidelines for HF management.\textsuperscript{7} The present results undoubtedly pave the way for clinical application of closed-loop automated control of hemodynamics in HF in future.

References


![Figure 2. Time courses of hemodynamic control by the developed system](image-url)