Automated Cardiovascular Drug Infusion System to Control Hemodynamics

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Abstract In the management of patients with unstable hemodynamics as seen in myocardial infarction or after cardiac surgical procedures, cardiovascular drugs such as inotropes and/or vasodilators are commonly infused to control systemic arterial pressure and/or cardiac output. 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. Closed-loop systems to automate drug infusion have been developed to facilitate this process. In the clinical setting, although closed-loop control of hemodynamics has been suggested to be useful and improve patient outcomes, this approach has not yet been widely adopted. In this review, we introduce several closed-loop systems that have been developed so far and our novel approach to control overall hemodynamics, address issues in their clinical application, and discuss future perspectives in this field.

Keywords: closed-loop control, cardiovascular drug, hemodynamics.


1. Introduction

In the management of patients with unstable hemodynamics, cardiovascular drugs such as inotropes, vasoconstrictors, vasodilators, diuretics and/or volume expanders are used to control systemic arterial pressure (AP), cardiac output (CO) and/or venous pressures. To obtain optimal outcome in individual patients, physicians adjust the infusion rates or doses of these drugs manually. This is a difficult and time-consuming process, especially in managing critically ill patients. Closed-loop systems to automate drug infusion have been developed to facilitate this process. Some previous studies suggest the potential clinical utilities and benefits of closed-loop control of those drugs. However, they have not yet been accepted widely in routine clinical practice. In this review, we present several closed-loop systems developed so far. We also introduce our novel approach to control overall hemodynamics using physiological model of cardiovascular dynamics. We finally address issues in the clinical application of the closed-loop drug infusion systems, and discuss future perspectives in this field.

2. Closed-loop control of cardiovascular drug infusion

Systemic AP is the most important hemodynamic variable for the maintenance of adequate blood supply to cerebral and coronary circulations. Closed-loop drug infusion system used to titrate vasodilator infusion to control AP is the prototype of all closed-loop cardiovascular drug infusion systems. Hypertension observed after cardiac surgery can cause serious complications such as bleeding and myocardial ischemia. Strict control of AP is mandatory in this setting. The fast-acting vasodilating drug, sodium nitroprusside (SNP), is used to treat patients with postoperative hypertension. The rapid and powerful action of SNP imposes upon physicians and nurses the task of frequent monitoring of AP followed by adjustment of SNP infusion rate. Because medical staff has many other duties, inappropriate or inadequate SNP infusion rate adjustment may occur. To improve the quality of patient care, automatic closed-loop control of SNP delivery systems have been developed [1, 2]. A proportional-integral-derivative (PID) controller of SNP infusion was first built and used clinically in the mid-1970’s [Fig. 1A] [1]. Closed-loop control of AP with SNP is more precise and stable than manual control. Chitwood et al. [2] demonstrated that compared with manual control, closed-loop control of postoperative hypertension using the PID controller significantly improved patient outcome as indicated by reduced transfusion requirement and less postoperative blood loss.

Other than the PID method, various control algorithms have been developed. The rule-based controller implements a set of expert rules in an “if-then” format to determine controller actions [3, 4]. These controllers are often combined with other controllers such as PID controllers. Hoeksel et al. [4] developed a closed-loop system for simultaneous control of AP and pulmonary artery blood pressures (PAP) during cardiac surgery. Their multiple-drug closed-loop system integrates five single-drug blood pressure controllers. Each drug controller uses the proportional-integral (PI) algorithm. Arterial hypertension is controlled using SNP or nitroglycerin;
arterial hypotension is controlled using noradrenaline or dobutamine; and pulmonary hypertension is controlled using nitroglycerin. The multiple-drug closed-loop system has a set of priority rules that automatically activates the optimum single-drug controller for each hemodynamic state. Drug infusion rates of the non-active controllers are kept constant. Knowledge of expert anesthesiologists was used to construct the priority rules. Their multiple-drug closed-loop system satisfactorily controlled both AP and PAP during cardiac surgery.[4].

Following the invention of the fuzzy set theory in 1965, fuzzy control systems to provide closed-loop control of SNP or noradrenaline infusion to normalize AP have been developed and used in patients [5, 6]. Fuzzy controllers are based on the if-then rule and can be designed using control operator’s (expert) knowledge and experience (Fig. 1B). Instead of allowing only the logical values of “true” and “false”, the degree of truth is allowed. Linguistically, we are used to dealing with these partial truths; clinicians have little trouble understanding what is meant by “AP is a little high.” Fuzzy logic allows the same approach in the closed-loop hemodynamic control. Merouani et al.[6] applied conventional fuzzy logic principles to modify intravenous norepinephrine (noradrenaline) infusion rates in septic patients. Use of the fuzzy controller was not harmful to patients, and was associated with reduction in duration of sepsis and total amount of norepinephrine infused [6]. Although the design of the fuzzy controllers does not require mathematical modeling of the response of AP to drug infusion, the parameters of the fuzzy controller must be tuned rigorously to appropriately deal with a wide range of clinical scenarios.

The inter- and intra-patient variabilities of drug responses can be serious problems if the parameters of the controllers are determined on the basis of population-averaged responses. To overcome this problem, model adaptive controllers have been developed [7, 8]. The adaptive controllers update on-line the patient’s parameters, specifying the drug responses using recursive least square method and/or from multiple model bank. Adaptive controllers (or self-tuning controllers) do not function well under noisy conditions such as during surgical procedures, because the noise signals are erroneously processed as a part of the variation of drug responses. Furutani et al.[9] developed a closed-loop drug infusion system to normalize AP during a surgical operation. Their system controls the infusion of the hypotensive drug, trimethaphan camsilate, by a state-predictive servo controller. The parameters of the controller are determined based on the dose-response characteristics of individual patient, which is identified at the beginning of the operation using a rectangular test signal (system identification). They applied their closed-loop system to patients undergoing total pelvic exenteration, the most extensive pelvic surgery. Their system precisely and stably controlled AP during the operations, and succeeded to reduce blood loss and operation times significantly.

The systems described above succeeded in controlling AP alone, AP and PAP simultaneously, or AP and CO simultaneously [1–10]. However, no closed-loop system developed so far is capable of controlling the overall hemodynamics; i.e., controlling AP, CO and left heart filling pressure such as left atrial pressure (LAP). These three hemodynamic variables are important and should be controlled simultaneously to within normal ranges in the management of patients with unstable hemodynamics. All the closed-loop systems presented above attempt to control the hemodynamic variables by estimating the apparent response of the variable to drug infusion. As

![Fig. 1](image-url)  
**Fig. 1** Examples of controller types.  
$e(t)$ is difference between the target and the measured output value.
shown in Fig. 1, the drug controllers determine the drug infusion rates based on the difference (e_1(t)) between target and measured values of AP (PAP or CO). However, it is difficult to expand them to simultaneously control AP, CO and LAP. In the systems that control AP and CO using inotrope and vasodilator [8, 10], all possible input-output relations have to be estimated; namely, inotrope-AP, inotrope-CO, vasodilator-AP, and vasodilator-CO relations. The reason for this is that these drugs affect AP and CO simultaneously to almost the same degree. If this approach is applied to simultaneously control AP, CO and LAP, at least nine input-output relations have to be estimated, because at least three drugs are required to independently control the three variables. This would make the system extremely complicated and therefore practically unfeasible. Furthermore, the input-output relations must be estimated in individual patients to tune the drug controllers, because the relations differ widely between patients and within patient over time. Even the direction of the output response can change. For example, in response to infusion of the vasodilator SNP, CO usually increases in patients with failing hearts, but may decrease in patients with preserved cardiac function [10]. The feasibility of individually estimating all possible input-output relations is questionable when drug infusion rates are allowed to vary simultaneously because of the difficulty to differentiate between drug effects [10].

3. Novel approach for closed-loop control of cardiovascular drug infusion

We have recently developed a new closed-loop drug infusion system to control AP, CO and LAP [11]. To overcome the difficulties described in the previous section, our system adopts a radically innovative approach. We have previously established a circulatory equilibrium framework by extending the Guyton’s classic framework. As shown in Fig. 2, the extended framework consists of an integrated cardiac output curve characterizing the pumping ability of the left and right heart, and a venous return surface characterizing the venous return property of systemic and pulmonary circulations [11]. The intersection point of the integrated CO curve and the venous return surface accurately predicts the equilibrium point of CO, LAP and right atrial pressure (RAP) (Fig. 2).

Once CO, LAP and RAP are predicted from the intersection point, systemic arterial resistance determines AP.

Based on this framework, instead of directly controlling AP, CO, and LAP, our system controls the integrated CO curve with dobutamine (DOB), the venous return surface with 10% dextran 40 (DEX) and furosemide (FM), and the systemic arterial resistance with sodium nitroprusside (SNP), thereby controlling AP, CO and LAP. The integrated CO curve is parameterized by the pumping ability of the left heart (S_l) [mmol·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]. They are related to a given set of AP, CO, LAP and RAP by the following equations [11]:

\[ S_l = CO/[\ln(LAP−2.03)+0.8] \]
\[ V = (CO+19.61RAP+3.49LAP) \times 0.129 \]
\[ R = (AP−RAP)/CO \]

**Figure 3** is a schematic illustration of our system. Once target values for AP, CO and LAP are fed into the system, it calculates the target values for S_l, R, and V using the above equations. The subject’s S_l, R, and V are calculated from measured AP, CO LAP and RAP values using the equations. To minimize the differences between target and subject’s S_l and R, PI controllers adjust the infusion rates of DOB and SNP, respectively. To minimize the difference between target and subject’s V, controllers based on if-then rule adjust the infusion of DEX or injection of FM. Thus, in contrast to the closed-loop systems presented in the previous section, our system determines the drug infusion rates based on the differences between target and measured values of the mechanical determinants of hemodynamics, i.e. S_l, R, and V (not the differences between target and measured values of AP, CO and LAP). **Figure 4** shows the experimental trial of our system in a canine heart failure model. **Figure 4A** shows the time courses of the infusion rates of DOB and SNP, and the cumulated volume of infused DEX. In this case, FM was not injected. **Figure 4B** shows the time courses of S_l, R and V. Infusion rates of DOB, SNP, and DEX were adjusted so that S_l, R and V reached their respective target values. By controlling the mechanical determinants of hemodynamics, the automated system controlled AP, CO and LAP accurately and stably (Fig. 4C).

The three drug controllers in our system (Fig. 3) are designed on the basis of only four input-output relations between drug infusion and response of the controlled mechanical determinants; namely, DOB-S_l, SNP-R and DEX/FM-V. The three closed loops are effectively
decoupled. Although there were inter- and intra-animal variabilities in the response of the mechanical determinants to drug infusion, the three drug controllers effectively compensate for these variations and did not require adaptive tuning in individual dogs. The variations of the response of the mechanical determinants to drugs may be small in comparison to that of the apparent response of the hemodynamic variables to drugs. At least, the directions of the responses of the mechanical determinants are consistent. For example, SNP decreases R both in subjects with and subjects without heart failure. Our system explicitly quantifies cardiac pump function, preload and afterload, thereby controlling the overall hemodynamics. This unique feature is intuitively appealing and is acceptable to medical practitioners, even if they are not trained in control engineering[11].

Fig. 3  Block diagram of a closed-loop drug infusion system for simultaneous control of systemic arterial pressure (AP), cardiac output (CO), and left atrial pressure (LAP). From target variables, target values of pumping ability of the left heart (SL), stressed blood volume (V), and systemic arterial resistance (R) are determined. Subject’s SL, V, and R are calculated from measured AP, CO, LAP and RAP. Proportional-integral (PI) controllers adjust infusion rate of dobutamine (DOB) and sodium nitroprusside (SNP) to minimize the difference between target and measured SL, and the difference between target and measured R, respectively. Rule-based controller adjusts infusion of 10% dextran 40 (DEX) or injection of furosemide (FM) so that the difference between target and measured V is minimized.

Fig. 4  Time courses of infusion rates of DOB and SNP, and cumulated volume of infused DEX (A), cardiovascular mechanical determinants (B), and hemodynamic variables (C) in 1 heart failure dog during closed-loop control of hemodynamics by our system. Broken horizontal lines in B indicate target values of the mechanical determinants. Broken horizontal lines in C indicate target hemodynamic variables. Drug infusion rates were adjusted so that the mechanical determinants reached the respective target values. As the determinants got closer to their targets, all 3 hemodynamic variables approached their respective target values.
Empirical constants used in our system such as the gains in PI controllers are derived from homogenous dogs. But, the sensitivities of the mechanical determinants to drug infusions may vary over an extensively diverse range of critically ill patients. Replacing the simple PI controllers in our system with the model adaptive controllers would render our closed-loop system robust in clinical application while preserving the unique feature and advantage of our novel approach.

4. Issues and future perspectives

The most important factor for effective hemodynamic control is that the variables such as AP and CO are monitored accurately. Furthermore, these variables should be measured with minimal invasiveness. AP monitoring is accomplished easily by placing catheters in peripheral arteries such as the radial artery. Easy monitoring may have facilitated the development and clinical application of closed-loop system to control AP. CO and LAP are commonly measured using the pulmonary artery catheter[12]. CO and LAP can be continuously and accurately monitored using pulse contour analysis of the pulmonary arterial pressure[13]. However, pulmonary arterial catheterization is invasive and requires technical skills. Several minimally invasive techniques have been developed, such as the pulse contour analysis of the peripheral arterial pressure for CO monitoring or the tissue Doppler imaging echocardiography for LAP monitoring[14,15]. However, the reliability of these monitors is controversial. We have recently developed a minimally invasive CO monitor, which utilizes the aortic flow velocity obtained by echocardiography and peripheral arterial pulse contour[16]. Experimental results have validated the reliability of our CO monitor. Application of our CO monitor may facilitate closed-loop control of CO in addition to AP, and also the overall hemodynamic conditions.

Despite the potential utility as reported by previous studies, there are many challenges facing the clinical application of the closed-loop drug infusion systems. Such challenges include, for example, addressing safety, regulatory approval, and acceptance by practitioners.

Ensuring safety is the most important issue[17]. Closed-loop system must be fail-proof: even if they malfunction, they must behave in a way that does not harm the patient. In the infusion of hypotensive drug, this means no overdosing or stopping of infusion. The closed-loop system developed by Furutani et al.[9] is equipped with risk control algorithm. The algorithm not only prevents malfunction of the hypotensive drug controller, but also actively observes the overall patient conditions and navigates fluid replacement therapy and respiratory assistance. Recently, the Food and Drug Administration (FDA) enforced Class I recall of an open-loop volumetric infusion device with defects resulting in “inaccurate flow rates which may lead to patient harm due to over infusion”[18]. If appropriately designed, closed-loop controlled infusion device that operates according to “patient response” would provide effective safety “guardrails” to limit patient harm.

Regulatory approval of any medical device depends on the assessment of risk vs. benefit[18]. If no meaningful clinical benefit is demonstrated, any potential risk associated with a closed-loop drug infusion system would be unacceptable. Demonstrating a “clinically meaningful” benefit (improving survival, reducing the length of hospital stay, reducing cost, etc.) is critically important to ensure regulatory approval.

Some physicians may be concerned that the closed-loop drug infusion systems may completely take over the hemodynamic management. Some physicians may be reluctant to choose an easy alternative in the management of unstable patients. However, these concerns are irrelevant. Closed-loop drug infusion systems must be supervised by physicians and nurses while helping to standardize patient care[19]. The system can reduce the stress and work imposed on the medical personnel, allowing them to spend more time on other patient-related activities, thereby improving the quality of patient care.

Advances in telecommunication may permit remote supervision of the closed-loop drug infusion system in the future[20]. This may help bring a level of accuracy and safety that can only be provided by trained specialists to a remote location where no physicians are available. Shortage of doctors in rural areas is a serious social issue in Japan[21]. Shortage of doctors in developing countries is also a serious problem over the world[22]. Providing an alternative to specialists trained in hemodynamic management may rescue victims in relief operations during serious disasters. Future research and development of the closed-loop drug infusion system should aim not only to establish the system as an advanced medical technology but also to provide a useful technique in locations where even basic medical service is not available.

5. Conclusion

Previous experimental and clinical studies indicate that closed-loop cardiovascular drug infusion to control hemodynamics is potentially useful. However, a great deal of work remains. A truly collaborative effort between leaders in engineering and medical research as well as device manufacturers is mandatory for successful introduction of the closed-loop cardiovascular drug infusion system into clinical practice.

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References


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