

回中心付近で興奮前面がそれ自身の終末部と相互作用することにより生じると考えられる。さらに、ニフェカレント作用下では旋回中心から離れた領域においても興奮波前面と終末部との相互作用が生じ、興奮波の分裂から新たなリエントリーの旋回中心が形成される現象もしばしば観察された。ニフェカレント存在下のリエントリーの旋回周期は薬物添加前よりも延長し、1拍ごとに大幅な変動がみられた。また、旋回経路や旋回周期の大幅な変動に伴って、興奮間隙が一部の領域に一過性に出現した。このようなニフェカレント存在下の不安定なリエントリーは長く続きにくく、早期に停止することが多かった。

$I_{Kr}$ チャンネル遮断薬存在下の心室筋二次元リエントリーの特徴は、以下のようにまとめることができる。①リエントリーの旋回経路や旋回周期が延長する。②不規則なさまよい運動を大きくしてリエントリーを著しく不安定にする。③興奮波の分裂を促進する。

$I_{Kr}$ チャンネル遮断薬はNaチャンネル遮断とは対照的に、興奮波の動的不安定性を高め、リエントリーの旋回を不規則にする。このため、単一の安定したリエントリー(mother rotor)によって維持されるタイプの頻拍や細動では、 $I_{Kr}$ チャンネル遮断薬はmother rotorの成立を妨げ、頻拍や細動の停止を促す<sup>19)</sup>。一方、 $I_{Kr}$ チャンネル遮断薬は興奮前面とその終末部との相互作用の機会を増して興奮波の分裂を促進する作用も有し、多数の独立した興奮波からなる(multiple wavelet)タイプの細動への移行を促進する。しかしながら、 $I_{Kr}$ チャンネル遮断薬作用下では興奮波長が延長しており、リエントリーが成立するためには大きな経路を必要とするため、興奮波分裂によって生じた新たな旋回中心が形成されても、興奮波が旋回する間に非興奮障壁や他の興奮波と衝突して消滅してしまうことが多い<sup>19)</sup>。特に、興奮波長に対する心筋組織の大きさが比較的小さい場合には(本研究で用いたウサギ心臓の二次元灌流標本などでは)この効果が大きく、興奮波の分裂がしばしば生じるにもかかわらず、頻拍や細動は早期に停止することが多い。しかし、心筋組織量が大きい場合には細動が持続しやすくなると考えられる。

## V おわりに

機能的リエントリーのダイナミクスと抗不整脈薬の作用について、ウサギ摘出心二次元灌流標本の光学マッピング実験の結果を中心に概説し、イオンチャンネル抑制による機能的リエントリーの停止機序について考察した。本研究では薬物の作用を論理的に解析するため、できるかぎり単純な実験系(正常動物から摘出した心臓の心室筋二次元灌流標本)を用いて検討した。しかし臨床における不整脈は、さまざまな基質的異常(梗塞や線維化巣、電気的リモデリング、細胞内Ca調節や代謝系の変化など)や、虚血、心不全、自律神経・体液因子の異常に伴って発生する。このような病態下の心臓における不整脈ダイナミクスや抗不整脈薬の作用については、モデル動物を用いた実験などによりさらに検討することが必要である。

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# SIMULTANEOUS DETECTION OF WAVE PROPAGATION VELOCITY AND DIRECTION IN OPTICAL MAPPING DATA OF CARDIAC EXCITATION USING OPTICAL FLOW

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It is important for analysis of wave propagation to obtain both velocities and directions of a wavefront at a given point when we investigate reentrant activities obtained by optical mapping technique using voltage sensitive dye. Although action potentials and Isochronal Map have been used for analyzing dynamics of reentry, neither of them can show instantaneous velocities and directions of wave propagation at a local region. Optical flow is a mathematical method to obtain distribution of apparent velocities of movement of brightness patterns in an image. It can determine the moving object's instantaneous velocity and direction simultaneously. It has been used in robotic vision and biomedical image analysis. Assuming that wavefront region of cardiac excitation moves as a continuous object, optical flow was applied to obtain wave propagation velocity and direction at a given point in optical mapping data of a perfused rabbit heart. Velocities and directions of a wavefront and during reentrant activities could be calculated in consistent with shape of reentry. The obtained velocities and directions of a wavefront computed by optical flow agreed well with that obtained from isochronal map derived from the same data.

## 1. Introduction

Optical mapping has been widely used in analyzing the dynamics of cardiac excitation wave propagation. Cardiac excitation was visualized using a high-speed digital video camera system with 1ms time resolution and 0.1mm space resolution. Isolated Langendorf perfused rabbit heart stained with voltage sensitive dye di-4-ANNEPS (2 $\mu$ M) was used. To reduce tissue contraction, 2,3-butandion monoxime (15 $\mu$ M) was used. Excitation light (500nm) illuminated the preparation and high-speed digital video camera (Fascam, Photoron) were used to map fluorescence from the preparation. The fluorescence was filtered through long-pass filter (600nm) to obtain fluorescence shift.

Isochronal map is a typical way of representing the spatio-temporal characteristics of cardiac excitation wave propagation. However, it is difficult to determine the velocity and direction of wave propagation directly from

isochronal map. The method to detect the velocity and direction of wave propagation in optical mapping data has been unknown.

Optical flow [1] is the method to estimate the vector field of objects in time series data. It is a typical way to detect the velocity and direction of moving solid objects using present optical flow. However, it is difficult to tract the movement of deformable image such as cardiac excitation wave propagation using present optical flow. A new optical flow method is needed to estimate the velocity and direction of cardiac excitation wave propagation.

Bayly *et al.* [2] have developed the method to estimate conduction velocity vector fields from epicardial mapping data. Their method was applied to simulation data and electrode array mapping data. To estimate the velocity and direction of wave propagation, active wave front was fitted using a least-squares algorithm to a smooth polynomial surface. However, it is difficult to apply Bayly's method to our experiment data directly because our optical mapping data(256×256pixels) are lager than simulation data(downsampled to 20×20 and 23×23 and epicardial electrode array data(23×23points) they used.

To detect the velocity and direction of cardiac excitation wave propagation in optical mapping data, we developed a new optical flow's method using a spatio-temporal volume [3] of optical mapping data.

## 2. Methods

To determine the velocity and direction of wave propagation, we used a spatio-temporal volume and Bayly's method. First, a spatio-temporal volume was used to obtain activation time in optical mapping data. A Spatio-temporal volume is x-y-t three-dimensional image obtained by piling up two-dimensional time-series data. After filtering the spatio-temporal volume, the spatio-temporal volume was cut to make x-t cross-sectional view and y-t cross-sectional view. Each cross-sectional view was binarized at 50% depolarization. By searching the boundary of the bright area and dark area on the y-t cross-sectional view, we can determine the activation time  $T(x, y)$  for the given coordinates of  $(x_i, y_j)$ . The slope of the activation time line on the cross-sectional view indicates the speed of wave propagation. The direction of wave propagation is obtained by the set of x-t cross-sectional view and y-t cross-sectional view. (Fig. 1)

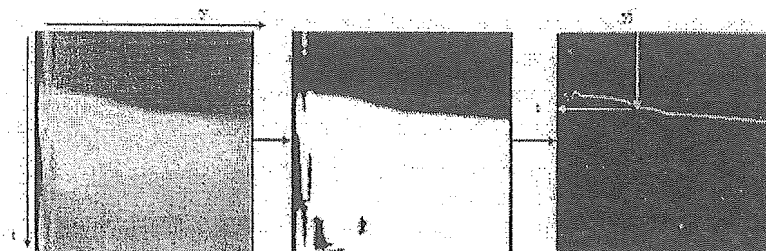


Figure 1. Spatio-temporal cross-sectional view(left), binarized image(middle), activation time(right).

Next, we used Bayly's method to determine the velocity and direction of wave propagation. The gradient of activation time  $\left(\frac{\partial T}{\partial x}, \frac{\partial T}{\partial y}\right)$  was found analytically in spatio-temporal cross-sectional view. The velocity vector  $(u, v)$  of a point on a wavefront is calculated as follows.

$$u = \frac{T_x}{T_x^2 + T_y^2} \quad v = \frac{T_y}{T_x^2 + T_y^2}$$

where  $T_x = \frac{\partial T}{\partial x}$  and  $T_y = \frac{\partial T}{\partial y}$ . If  $T_x^2 + T_y^2 = 0$ , then  $u$  and  $v$  are not calculated. [2]

### 3. Results

Our developed method was applied to typical types of wave propagation in optical mapping data such as a planar wave and a spiral wave. Figure 2 shows a planar wave in our optical mapping data. Cardiac excitation propagates from the apex of the heart to the base of the heart. Figure 3(left) shows an isochronal map using a spatio-temporal volume. Figure 3(middle) shows a direction map that the color on wavefronts indicates the direction of wave propagation. Figure 5(right) shows a velocity map that the color on wavefronts indicates the speed of wave propagation. As shown in Fig.3, the shape of the wavefront turns into the shape of U because the wavefront propagates slower on the center of the heart than on the other area of the heart.

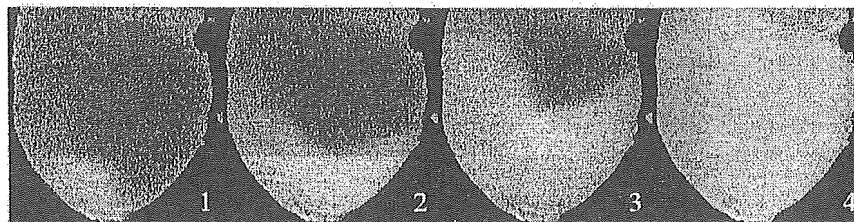


Figure 2. Planar wave in optical mapping data.

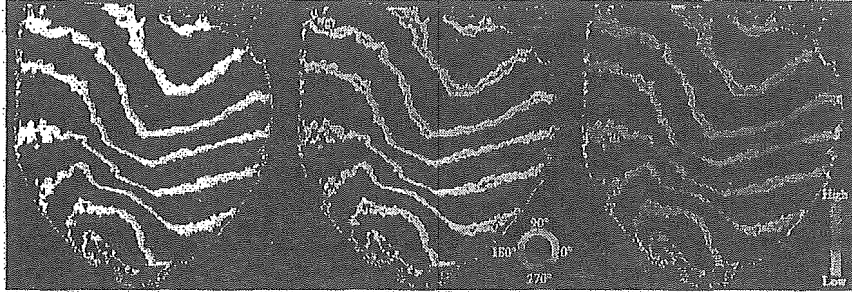


Figure 3. Isochronal map(left), direction map(middle), velocity map(right).

Figure 4 shows a spiral wave in our optical mapping data. The wavefront circulates around the center of the heart in a clockwise direction. Figure 5(left) shows an isochronal map. Figure 5(middle) shows a direction map. Figure 5(right) shows a velocity map. The wavefront propagates slower near the core of spiral reentry than on the other area of the heart(Fig.5).

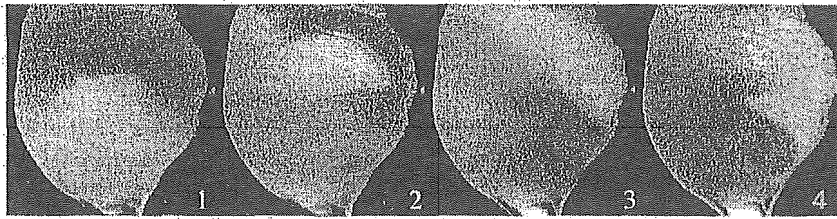


Figure 4. Spiral wave in optical mapping data.

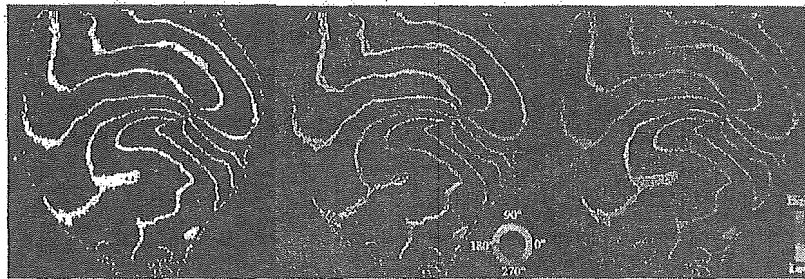


Figure 5. Isochronal map(left), direction map(middle), velocity-map(right).

#### 4. Discussion

The velocity and direction of wave propagation in optical mapping data were estimated using spatio-temporal volume and Bayly's method. As a result, the velocity and direction of wave propagation were obtained not only for simple movement such as a planar wave but also for complex movement such as a spiral



wave. The direction and velocity of wave propagation by our method were agreed well with the direction and velocity of wave propagation from an isochronal map qualitatively.

Some lines on an isochronal map by our method have width because of digitalization that data of images are used as integer value. The faster a wavefront propagates, the more cardiac cells are calculated to be active at the same time and the larger the width of a wavefront becomes. The reason why the velocities on the boundary of the wavefront and inside of the wavefront were different is that activation time function becomes stair-like function by digitalization. The gradient of activation time function is calculated to be 0 when a wavefront propagates faster than sampling rate. To modify the problem, we need to calculate the gradient of a wavefront from a wider range of a wavefront in spatio-temporal cross-sectional views.

In this study, we detected the velocity and direction of a wavefront in optical mapping. Not only a wavefront but also a wavetail in optical mapping can be detected by binarization at appropriate threshold in spatio-temporal cross-sectional views.

## 5. Conclusion

We developed a new optical flow's method to detect the velocity and direction of wave propagation in optical mapping data using a spatio-temporal volume. Spatio-temporal cross-sectional views were used to detect activation times. To calculate the direction and velocity of wave propagation, Bayly's method was expanded to our method. The velocity and direction of wave propagation were obtained directly from a velocity map and a direction map. Our new method will be useful to analyze the dynamic of wave propagation in optical mapping data.

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# 第17章 人工臓器を支える要素技術

## 1. 生体を超える人工臓器制御

はじめに

人工臓器の進化は著しく、装置の小型化・高効率化が進み、体内に埋め込んで普通の生活を行うことが可能になりつつある。このような人工臓器では、手動調節を極力減らした自動制御や人工臓器装着者がより安楽に快適に過ごすことができるための制御が望まれている。しかしながら、生体の制御系の主なものは神経系や体液性などの多重フィードバックにより複雑な制御を行っており、それを限られたセンサ情報のみを使用する人工臓器で再現することはきわめて困難である。現在、生体の臓器制御特性の解明、センサ技術の向上、推定理論の導入などにより、より生体に近い制御の開発が進んでいる。

一方、人工臓器制御には、生体と同様の機能を実現する他にも、生体が本来持っていない以下の機能を実現することで人工臓器を適用することの有利性を向上させる可能性がある。

① 人工臓器本体だけでなく生体側の状態の把握と異常を検出

② 装着者の個人差や状態変化へのすばやい適応

③ 治療や健康維持を意識した制御法の導入

上記すべてを兼備した制御こそ、生体を超える人工臓器制御法の1つの姿であると考えられる。残念ながら現在のところ、このような制御法はいかなる人工臓器においても実現されてはいない。しかし、それぞれの機能を実現するための要素技術の研究は各機関で進められている。

本稿では、人工心臓の制御を題材として、上述した機能を実現させるための要素技術について述べる。

### 1.2 状態モニタリングと異常の検出

人工臓器の制御において、制御システムは装置および生体の状態をできるだけ正確に把握することが望ましい。特に人工心臓のように装置の異常がすぐに生命の危機にかかわる場合にはきわめて重要な問題の1つと言える。さらに、異常は人工臓器だけで起こるので

はない。例えば、補助人工心臓を装着している生体における突然の心停止や血栓による梗塞などである。このような異常状態をできるだけ早いうちに発見し、対策を行うことができれば、人工臓器の故障や突発的な病状の変化への不安感を軽減することができる。また、人工臓器の長期の使用や治療を視野に入れている場合には、生体の生理的、機能的変化を的確にとらえることは病状の進行、治療効果、適切な制御法の選択等に大きく貢献すると考えられる。

筑波大学のグループでは、人工心臓を用いて個々の生体に適応したより効果的な医療行為や治療制御を行うことを目的として体循環系をモデル化し、そのパラメータをリアルタイムに同定する手法を提案している<sup>1)</sup>。循環系をモデルとしてとらえ、そのパラメータを推定することにより、センサから得られる計測値の異常だけでなく、血管抵抗や動脈系コンプライアンスといった生理的なパラメータも評価可能となる。さらに同グループは、このような状態推定システムを備えたインターネットを利用した遠隔モニタリングシステムも開発している。

異常状態は基本的にその発生確率が低いことや事前に予測不可能な異常状態が少なからず存在するため、予め異常時の各センサの状態をデータベース化してそれを参照しながら状態診断を行う方法には限界がある。また、異常診断法の主なものは各センサの値に閾値を設けその範囲を逸脱したことで検出するものがほとんどであり、異常の予兆をとらえることは困難である。異常の中にはセンサから得られる波形にその予兆が現れていることが少なくなく、その予兆を検出できれば致命的な状態になる前に対策を施すことができる可能性がある。東北大学のグループでは自己組織化マップ (Self-Organizing Map ; SOM) を利用し、センサ情報から状態を自動分類することにより異常検出を行う方法を提案している<sup>2,3)</sup>。この方法はいわば熟練の医者が波形を見て“違和感”を感じることで異常を検出するような診断法に似ており、過去のデータベ

ースに存在しない異常であっても“正常でない”ことによる診断が可能である。自己組織化マップは、Kohonenにより1981年頃に発表された教師なし学習ニューラルネットワークで、入力パターン群をその類似度に応じて分類する能力を自律的に獲得していくニューラルネットワークである。SOMに対して計測データ1拍分の血圧データを入力ベクトル化してネットワークに入力し学習させ、学習後に対応する状態をラベル化した結果が図17.1.1である。それぞれの状態ごとに対応するニューロンが集まっているのがわかる。学習後のSOMに1拍ごとに計測データを入力することで現在の状態を推定することが可能である。また、このように同じ状態を表すニューロンが自動的に集まって分布する（自己組織化）ことを利用して、明確な異常状態になる前に異常の予兆をとらえることができる可能性がある。

1.3 生体への適応と最新の制御理論の応用

人工臓器の制御の目標が定まったとしても、それを実現するためには制御パラメータのチューニングが必要になる。人工臓器の本体は基本的に同一ではあるが、それを埋め込む生体は個人差があることはもちろん、術後の回復期や成長、体質変化などのように生体の特性は時間的に変動すると考えられる。そのため制御パラメータはそれぞれの個体もしくは状態に合わせて調節しなければならない。すなわち、人工臓器制御には制御対象の個人差および時間変化に自動的に対応した制御の実現が望ましい。

生体の状態変化にきめ細かく自動的に対応するような制御を行うための手法として、適応制御、学習制御、ハイブリッドシステム等の制御理論の導入が進められている。

1.3.1 適応制御理論を使用した人工心臓制御

適応制御とは制御対象の特性が未知であっても、制御系中に制御対象をモデルとして推定する機構を持たせ、常に制御パラメータそのものを変化させて系全体が常に理想的な特性を維持して制御目的を達成しようとするものである。

東北大学グループでは、東京大学グループで提案された1/R制御に適応制御理論を導入することで、1/R制御の数式モデルに含まれるパラメータの試行錯誤的決定をある程度回避できることを示した。

提案された適応制御法では、図17.1.2に示すように、完全人工心臓（TAH）駆動下の生体循環系C（制御対象）を2入力-2出力システムであると単純化してモデル化している。すなわち、Cへの入力が人工心臓の操作量X（拍動型人工心臓の場合は駆動周期、遠心ポンプではモータ回転数）と末梢血管抵抗（R [mmHg・min・kg/L]）であり、出力が平均大動脈圧（AoP [mmHg]）と心拍出量（CO [L/min]）である。また、BはTAHの制御装置であり、AoP、その目標値AoP\*\* およびRから操作量を決定するものである。

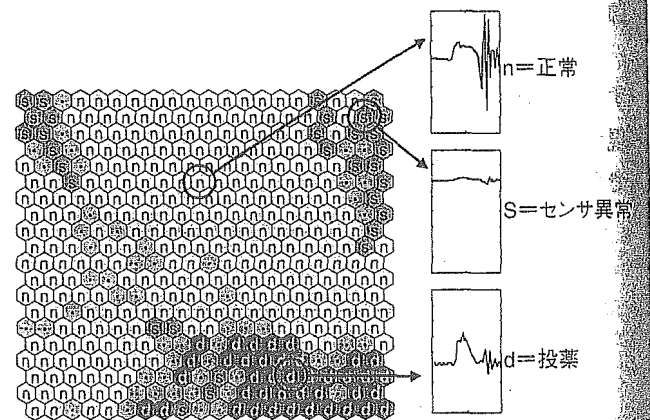


図 17.1.1 学習後のSOMに対応する状態のラベルを付したマップ

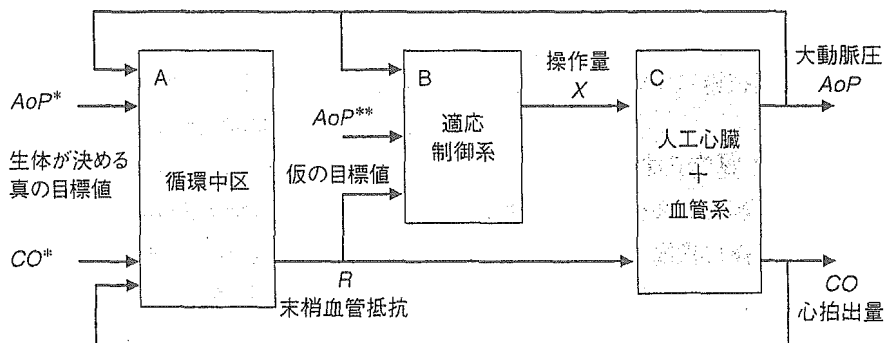


図 17.1.2 末梢血管抵抗型適応制御

ここで、制御装置は  $R$  が変化してもその影響が  $AoP$  に現れないように操作量を調節する制御を行う。具体的には、2 入力・1 出力システム ( $CO, R$ )  $\rightarrow$   $AoP$  に対する確定的自己回帰移動平均 (DARMA) モデルを逐次同定し、 $R \rightarrow AoP$  の影響をキャンセルしつつ、 $AoP$  を  $AoP^{*}$  に近づける非干渉化適応制御系を構築する。このとき、 $A, C$  を含むシステムが常に安定を保つように制御器のパラメータを調節する。

モック循環系でこの末梢血管抵抗依存型適応制御法を適用したときの、定常流型人工心臓と拍動流型人工心臓の応答波形の比較したものが図 17.1.3 である。どちらの場合も、200 ~ 300s の間でバルブの開度を大きくすることにより  $R$  を減少させている。これに応じて制御電圧もしくは拍動数は自動的に増大し、 $AoP$  が目標値 90 mmHg に定値制御されていることがわかる。

このように適応制御の導入によって生体の個人差や循環特性の時間的変化に対応できるだけでなく、同様

の制御を異なるポンプに対しても適応することが容易になると予想される。

### 1.3.2 知的制御

一般に制御パラメータの決定は、制御対象の特性が既知であることが望ましい。しかし生体は複雑な非線形システムであるため、制御対象を正確に数式モデルとして表すことは困難である。したがって、制御パラメータの最終的なチューニングには試行錯誤を行うことが多い。

知的制御とは、ニューラルネットワーク、ファジ理論、学習、遺伝的アルゴリズムなどのソフトウェアアルゴリズムを使用した制御手法である。このような制御の特徴として、制御モデルやコントローラを構築する際に、物理的性質に基づく情報を必要としないところにあると言える。すなわち、制御パラメータのチューニングをこのような理論を利用することにより複雑なシステムに対しても、自動的に制御パラメータの最適化を行えると期待できる。

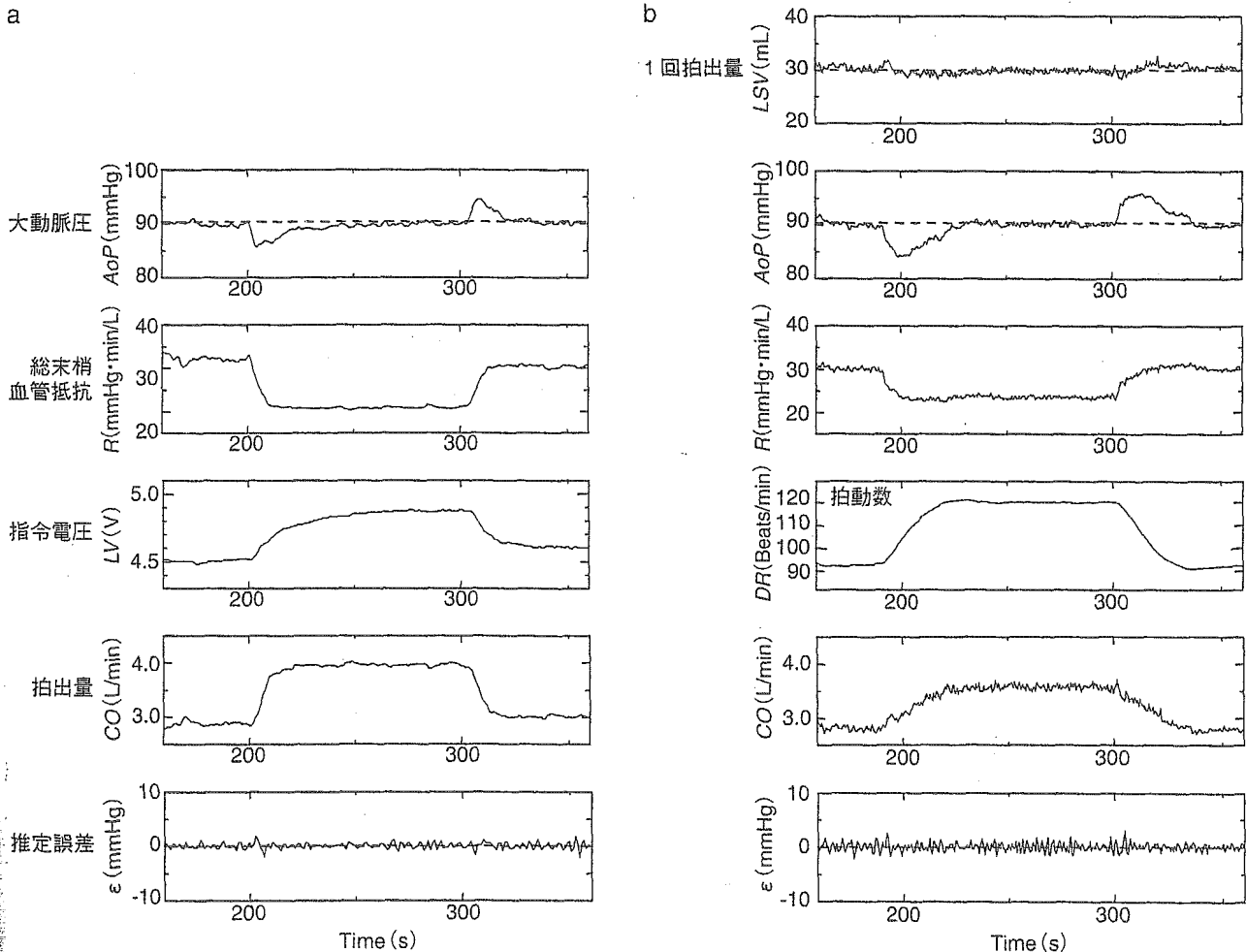


図 17.1.3 末梢血管抵抗依存型適応制御法を定常流型人工心臓と拍動流型人工心臓に適用した際の制御結果  
 a : 定常流型人工心臓      b : 拍動流型人工心臓

近年、知的制御の1つである強化学習理論を応用した制御の研究が注目を浴びている。強化学習とは、試行錯誤を通じて環境に適応する学習制御の枠組みである。教師付き学習とは異なり、状態入力に対する正しい行動出力を明示的に示す教師が存在しない。その代わりに報酬というスカラーの情報を手がかりに学習を行う。つまり、報酬が適当に設定されていれば人間が行うよりも優れた制御方法を発見する可能性があるのである。現在のところ、強化学習を人工臓器の制御に適用した例は報告されていないが、マニピュレータの制御やコミュニケーションロボット、サッカーロボットの協調動作等への応用が行われている。どのように学習を行うか、報酬をどのように定義するか等解決すべき課題も多いが、このような制御を人工臓器の制御に応用することで、生体の循環制御中枢と協調して制御を行うような制御の実現が期待できる。

### 1.3.3 ハイブリッド制御

人工臓器を制御する場合、それぞれの状態に合わせて制御アルゴリズムを切り替える必要がある場合がある。人工臓器の制御においても生理的な循環制御だけでなく、術後の不安定な状態、心房もしくは心室壁の脱血カニューレへの吸着時、補助人工心臓における心停止状態など、それぞれの状態に合わせた複数の制御アルゴリズムが必要になる。複数の制御アルゴリズムを切り替える場合、それぞれの制御が安定に行われることはもちろんのこと、安定に切り替えが行われる必要がある。このようにいくつかの連続時間動的システムと離散事象を組み合わせたシステムをハイブリッドシステムと呼び、ハイブリッドシステムの制御系設計や安定解析が注目を集めている。現在のところ人工臓器への応用例は報告されていないが、飛行管制、エンジン制御、ロボット制御への応用研究が行われている。

## 1.4 治療および健康維持を考慮した制御

### 1.4.1 補助人工心臓におけるブリッジ to リカバリ

補助人工心臓の使用目的として、移植までのつなぎとしての使用の他に、循環補助により心臓の負荷を軽減することでその間の心臓の治療・回復を期待する治療手段としての利用が注目されている。実際にいくつかの症例では離脱に成功が報告されている<sup>5)</sup>。

補助人工心臓の生理的循環制御がそのまま自然心臓の治療に効果的であるとは限らない。一般に、心室脱血の補助人工心臓装着時においては、自然心臓にある

程度の循環調節能力が残されている場合、補助人工心臓の流量を変化させても総血流量はあまり変化しない。すなわち、補助人工心臓の駆出流量を最小限に抑えて補助を行うことで生体の循環制御に任せることが可能である一方で、補助率をできるだけ上げることで心臓への負荷をできるだけ軽減することも可能である。実際に補助率の差が心筋酸素消費に影響があることが報告されている<sup>6)</sup>。どのような流量制御が心筋の回復に最も効果的であるかは解明されていないが、人工心臓の制御法として、生理的な循環制御の他に自然心臓の治療・回復を考慮した制御を採用することでより効率的に自然心臓の回復をサポートできる可能性がある。

補助人工心臓を自然心臓の治療を目的として使用した場合、人工心臓からいつ離脱したらよいか問題になる。すなわち、自然心臓の機能を的確に把握することが重要である。補助人工心臓装着時の心機能推定の方法として、人工心臓用モータの電流波形から心室圧の最大値を推定しその値により評価する方法<sup>7)</sup>や、心機能の評価法として知られている最大エラストランス  $E_{max}$  を拍ごとに推定する方法<sup>8)</sup>が提案されている。

### 1.4.2 人工心臓で臓器血流をコントロール

人工心臓が発生する血流パターンが自然心臓が発生するものとは異なることを積極的に利用して、臓器への血流分配をコントロールする研究が行われている。

東北大学のグループでは、同グループが開発した10～50 Hzの振動流を生み出すことができる振動流ポンプ(VFP)によって、総血流量を変えずに脳への血流量が増加したことを報告している<sup>9)</sup>。流量パターンによって血液配分が変化する理由についてはまだ明らかにされていないが、もしこのような現象が血管のインピーダンスに起因するならば、各臓器の血流に対する周波数特性を調べることによって特定の部位の血流量を制御できる可能性がある。

各臓器の血流の制御が生体にどのような影響を与えるのかは未解明ではあるが、薬剤によって特定の部位の血流量を増加させることで症状を改善する治療が行われている現状を考えると、人工心臓の制御によって治療を行うことが可能なのかもしれない。人工心臓用のポンプがさらに小型・高効率になり、体の各部にポンプを埋め込むことができるようになることを考慮して、血流を分散制御する研究も始まりつつある<sup>10)</sup>。

## 1.5 おわりに

本稿では、生体を超える人工臓器制御について、主

に人工心臓を題材として、実現のための要素技術について紹介した。一般に人工臓器の開発はデバイスが中心であり、その制御法についての開発は後手になることが多いが、安全性、機能性、有効性に優れた制御法を開発することで人工臓器を単なる延命のための装置から治療あるいは健康維持のための装置に拡張させることが期待できる。

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(田中 明、吉澤 誠)

## TRANSLATIONAL PHYSIOLOGY

# 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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<sup>1</sup>Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Suita; <sup>2</sup>Research Division on Advanced Information Technology, Information Synergy Center, Tohoku University, Sendai; <sup>3</sup>Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Science, Fukuoka, Japan

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**Uemura, Kazunori, Atsunori Kamiya, Ichiro Hidaka, Toru Kawada, Shuji Shimizu, Toshiaki Shishido, Makoto Yoshizawa, Masaru Sugimachi, and Kenji Sunagawa.** Automated drug delivery system to control systemic arterial pressure, cardiac output, and left heart filling pressure in acute decompensated heart failure. *J Appl Physiol* 100: 1278–1286, 2006. First published December 22, 2005; doi:10.1152/jappphysiol.01206.2005.—Pharmacological support with inotropes and vasodilators to control decompensated hemodynamics requires strict monitoring of patient condition and frequent adjustments of drug infusion rates, which is difficult and time-consuming, especially in hemodynamically unstable patients. To overcome this difficulty, 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). Previous systems attempted to directly control AP and CO by estimating their responses to drug infusions. This approach is inapplicable because of the difficulties to estimate simultaneous AP, CO, and Pla responses to the infusion of multiple drugs. The circulatory equilibrium framework developed previously (Uemura K, Sugimachi M, Kawada T, Kamiya A, Jin Y, Kashihara K, and Sunagawa K. *Am J Physiol Heart Circ Physiol* 286: H2376–H2385, 2004) indicates that AP, CO, and Pla are determined by an equilibrium of the pumping ability of the left heart ( $S_L$ ), stressed blood volume (V), and systemic arterial resistance (R). Our system directly controls  $S_L$  with dobutamine, V with dextran/furosemide, and R with nitroprusside, thereby controlling the three variables. We evaluated the efficacy of our system in 12 anesthetized dogs with acute decompensated heart failure. Once activated, the system restored  $S_L$ , V, and R within 30 min, resulting in the restoration of normal AP, CO, and Pla. Steady-state deviations from target values were small for AP [4.4 mmHg (SD 2.6)], CO [5.4 ml·min<sup>-1</sup>·kg<sup>-1</sup> (SD 2.4)] and Pla [0.8 mmHg (SD 0.6)]. In conclusion, by directly controlling the mechanical determinants of circulation, our system has enabled simultaneous control of AP, CO, and Pla with good accuracy and stability.

computers; negative feedback; circulatory equilibrium

IN THE MANAGEMENT OF PATIENTS with acute decompensated heart failure after myocardial infarction or after cardiac surgical procedures, cardiovascular agents such as inotropes and/or vasodilators are commonly used to control systemic arterial pressure (AP), cardiac output (CO), and left heart filling pressure (2, 13, 20). Because 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. Several closed-loop systems to automate drug infusion have been developed to facilitate this process (10, 11, 18, 26, 27). Closed-loop control of AP with vasodilators was more precise and stable than manual controls (10, 11). Chitwood et al. (10) demonstrated that, compared with manual control, closed-loop control of postoperative hypertension significantly improves patient outcome by reducing the transfusion requirement and postoperative blood loss. Although closed-loop control of hemodynamics has been suggested to be useful in clinical settings, no closed-loop system so far developed is capable of controlling the overall hemodynamics; i.e., controlling AP, CO, and left heart filling pressure simultaneously (18). This is because all previous systems attempted to directly control the hemodynamic variable by estimating response of the variable to drug infusion (10, 11, 18, 26, 27). Although such an approach worked well in controlling a single variable, it cannot be applied to control of the three variables, because it is difficult to simultaneously estimate their responses to the infusions of multiple drugs.

In this study, we developed a new automated drug delivery system that is capable of controlling AP, CO, and left atrial pressure (Pla). We modeled the entire cardiovascular system by extending Guyton's framework of circulatory equilibrium (16, 17, 24, 25). As shown in Fig. 1, the extended 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 (24, 25). 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) (24, 25). Once CO, Pla, and Pra are predicted from the intersection point, systemic arterial resistance determines AP. On the basis of 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 the three hemodynamic variables.

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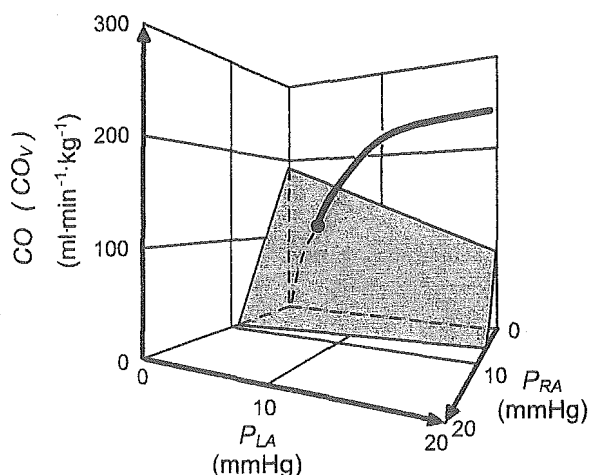


Fig. 1. Diagram of circulatory equilibrium for cardiac output (CO), venous return (CO<sub>v</sub>), left atrial pressure (P<sub>LA</sub>), and right atrial pressure (P<sub>RA</sub>). The equilibrium CO, P<sub>LA</sub>, and P<sub>RA</sub> are obtained as the intersection point of the venous return surface and integrated cardiac output curve. [Modified from Uemura et al. (Ref 25).]

The purpose of this study was, therefore, to develop and validate the new automated drug delivery system. We evaluated the efficacy of our system in a canine model of acute ischemic heart failure. Our results indicated that this novel automated drug

delivery system was able to control AP, CO, and P<sub>LA</sub> simultaneously with reasonably good accuracy and stability.

**METHODS**

*Cardiac Output Curve, Venous Return Surface, and Arterial Resistance*

On the basis of previous studies, we parameterized the integrated CO curve by the pumping ability of the left heart (S<sub>L</sub>), the venous return surface by total stressed blood volume (V), and the systemic arterial resistance by R (see APPENDIX A) (24, 25). Our system aims to control these cardiovascular parameters to achieve target AP (AP\*), target CO (CO\*), and target P<sub>LA</sub> (P<sub>LA</sub>\*).

*Automated Drug Delivery System*

Figure 2A illustrates a block diagram of the automated drug delivery system, using a negative feedback mechanism.

Target values of S<sub>L</sub> (S<sub>L</sub>\*), V (V\*), and R (R\*) are determined according to the AP\*, CO\*, and P<sub>LA</sub>\* (see APPENDIX B). The subject's S<sub>L</sub>, V, and R are calculated from the measured AP, CO, P<sub>LA</sub>, and P<sub>RA</sub> (Fig. 2A). S<sub>L</sub>, V, and R are compared with S<sub>L</sub>\*, V\*, and R\*, respectively.

To minimize the difference between S<sub>L</sub>\* and S<sub>L</sub> (ΔS<sub>L</sub> = S<sub>L</sub>\* - S<sub>L</sub>) and the difference between R\* and R (ΔR = R\* - R), proportional-integral (PI) feedback controllers adjust infusion rates of Dob and SNP, respectively (Fig. 2A). In the PI controller (Fig. 2B), ΔS<sub>L</sub> (or ΔR) and the difference integrated with an integral gain (K<sub>i</sub>) are summed and scaled by a proportional gain (K<sub>p</sub>) to give the infusion rate of Dob (or SNP). We determined values of K<sub>i</sub> and K<sub>p</sub> on the

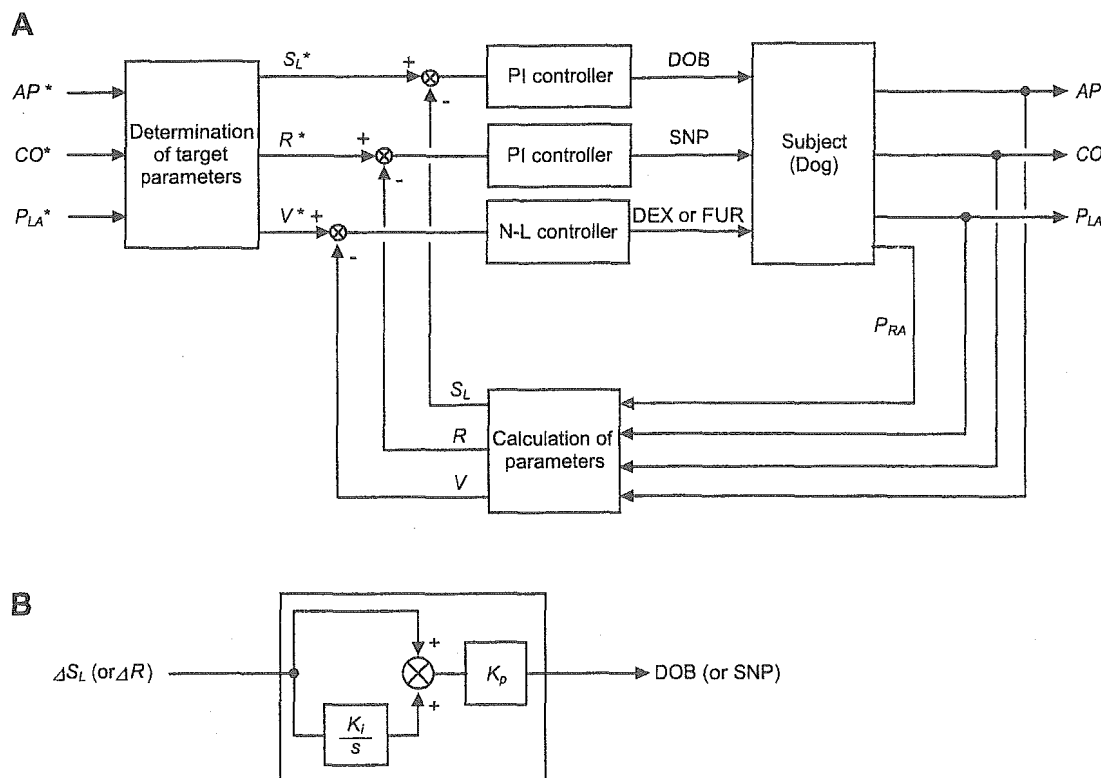


Fig. 2. A: block diagram of an automated drug delivery system for simultaneous control of systemic arterial pressure (AP), CO, and P<sub>LA</sub>. AP\*, CO\* and P<sub>LA</sub>\* represent target AP, target CO, and target P<sub>LA</sub>, respectively. From these target variables, target values of pumping ability of the left heart (S<sub>L</sub>\*), stressed blood volume (V\*), and systemic arterial resistance (R\*) are determined. Subject's S<sub>L</sub>, V, and R are calculated from measured AP, CO, P<sub>LA</sub>, and P<sub>RA</sub>. Proportional-integral (PI) controllers adjust infusion rate of dobutamine (Dob) and sodium nitroprusside (SNP) to minimize the difference between S<sub>L</sub> and S<sub>L</sub>\* (ΔS<sub>L</sub>), and the difference between R and R\* (ΔR), respectively. Nonlinear (N-L) controller adjusts infusion of 10% dextran 40 (Dex) or injection of furosemide (Fur) so that the difference between V and V\* is minimized. B: block diagram of the PI controller. K<sub>i</sub> and K<sub>p</sub> represent the integral and proportional gain constants, respectively; s is a Laplace operator.

basal of open-loop response of  $S_L$  (or R) to the infusion of Dob (or SNP) (4, 9).

To minimize the difference between  $V^*$  and  $V$  ( $\Delta V = V^* - V$ ), a nonlinear (NL) feedback controller (Fig. 2A) adjusts the infusion of Dex or injection of Fur on the basis of the following "if-then" rules:

Rule 1: If  $\Delta V \geq X_1$  ml/kg then infuse Dex ( $Y_1$ , ml/min)

Rule 2: If  $\Delta V \leq X_2$  ml/kg then inject Fur ( $Y_2$ , mg)

We determined values of  $X_1$ ,  $Y_1$ ,  $X_2$ , and  $Y_2$  on the basis of the open-loop response of  $V$  to the infusion of Dex and Fur.

These adjustment processes are repeated in parallel and continued until the differences disappear.

#### Preparation

We used 35 adult mongrel dogs in this study [both sexes, body weight 25 kg (SD 4)]. Care of the animals was in strict accordance with the guiding principles of the Physiological Society of Japan. All protocols were approved by the Animal Subjects Committee of the National Cardiovascular Center. Anesthesia was induced with pentobarbital sodium (25 mg/kg). Animals were intubated endotracheally. Isoflurane (1.0%) was inhaled continuously to maintain an appropriate level of anesthesia during the experiment. A catheter (8-Fr) was placed in the right femoral artery, which was connected to a pressure transducer (DX-200, Nihon Kohden, Tokyo, Japan) to measure AP. After a median sternotomy, a small pericardial incision was made at the level of the aortic root. Through the incision, an ultrasonic flow meter (20A594, Transonics, Ithaca, NY) was placed around the ascending aorta to measure CO. Fluid-filled catheters were placed in the left and right atria to measure Pla and Pra, respectively. They were connected to pressure transducers (DX-200, Nihon Kohden). The junction between the vena cavae and the right atrium was taken as the reference point for zero pressure. The undamped natural frequency and the damping ratio of the fluid filled catheters for the pressure measurements were 21 Hz and 0.22, respectively. A urinary catheter was inserted to measure urine volume.

A catheter (6-Fr) was placed in the right femoral vein. A roller pump (Minipuls 3, Gilson, Middleton, WI) was attached to the venous line to infuse Dex. A double-lumen catheter was also introduced into the right femoral vein for administration of Dob and SNP. Infusion pumps (CFV-3200, Nihon Kohden) were used for Dob and SNP infusion. The infusion rates of Dex, Dob, and SNP were controlled with a personal computer (MA20V, NEC, Tokyo, Japan) through a 12-bit digital-to-analog converter (DA12-8PCI, Contec, Osaka, Japan). A catheter (6-Fr) was placed in the right external jugular vein, from which Fur was injected after a command signal from the computer.

#### Experimental Protocols

We induced left ventricular failure (LVF) in all the animals by embolizing the left circumflex coronary artery with glass microspheres (90  $\mu\text{m}$  in diameter) (24, 25). We adjusted the amount of injected microspheres to increase Pla to more than 18 mmHg or decrease CO to less than 70  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ . When ventricular tachycardia or frequent premature ventricular contractions were noted, lidocaine (1 mg/min) was infused to suppress the arrhythmia.

**Response of cardiovascular parameters to drug infusion.** Under open-loop conditions, we examined the response of cardiovascular parameters to drug infusions in 21 dogs with LVF. In 10 dogs, we infused Dob in a stepwise manner at 6  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for 10 min to obtain a step response of  $S_L$ . In six dogs, we infused SNP at 2  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for 10 min to obtain a step response of R. In five dogs, we infused Dex at 0.4  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  for 10 min to observe the response of V. In seven dogs, we injected Fur (20 mg, bolus iv) and observed the response of V and urine volume for 50 min.

**Application of the automated drug delivery system.** We applied the system to the other 14 dogs with LVF. We first defined AP\* (90–105

mmHg), CO\* (90–100  $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ), and Pla\* (8–12 mmHg), which were fed into the system to determine  $S_L^*$ ,  $V^*$ , and R\* (see APPENDIX B). The controllers were then activated by closing the loops. In 12 dogs (*group 1*), we observed the performance of the system over 50–60 min. In two dogs (*group 2*), we observed the performance of the system over 100–150 min to evaluate stability of the closed-loop control over a longer periods of time.

With the use of the computer, analog signals of AP, CO, Pla, and Pra were digitized at 200 Hz with a 12-bit analog-to-digital converter [AD12-16U(PCI)E, Contec, Osaka, Japan] and stored on a hard disk for offline analysis. In the closed-loop control, the digitized signals were smoothed by a low-pass filter (time constant, 10 s) and were used as the system controlled variables. The infusion rates of Dob, SNP, and Dex were also stored. Urine volume after the injection of Fur was recorded.

#### Data Analysis

**Evaluation of the response of cardiovascular parameters and design of the controller.** We described the step response of  $S_L$  and R by a transfer function of a first-order model with a transport delay. In this model, change in  $S_L$  from baseline ( $\delta S_L$ ) in response to Dob infusion can be expressed by the following formula:

$$\delta S_L(t) = \begin{cases} G \cdot \left[ 1 - \exp\left(-\frac{t-L}{T}\right) \right] & (t \geq L) \\ 0 & (t < L) \end{cases} \quad (1)$$

where  $G$  is static gain [ $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}(\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1})^{-1}$ ],  $L$  is transport delay (s), and  $T$  is time constant (s). Change in R from baseline ( $\delta R$ ) in response to the SNP infusion can be expressed similarly and is characterized by  $G$  [ $\text{mmHg}\cdot\text{min}\cdot\text{ml}^{-1}\cdot\text{kg}(\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1})^{-1}$ ],  $L$  (s), and  $T$  (s). We estimated the parameters of the transfer function by approximating  $\delta S_L$  and  $\delta R$  to Eq. 1 using the least square method. We averaged the parameters of the transfer function of  $S_L$  response for 10 animals and those of R response for 6 animals. The averaged parameters were used to determine the PI gain constants,  $K_i$  and  $K_p$ , in accordance with the method of Chien et al. (9). Their method provides PI constants that permit the regulated variable to respond rapidly without overshoot (4, 9).

We evaluated the change in V from baseline ( $\delta V$ ) in response to the infusion of Dex and Fur. On the basis of  $\delta V$ , we determined the constants ( $X_1$ ,  $Y_1$ ,  $X_2$ , and  $Y_2$ ) of the if-then rules.

**Efficacy of the automated drug delivery system.** We calculated the following indexes to evaluate the accuracy and stability of the control of AP, CO, and Pla by the new system: the time required for the hemodynamic variables to reach the acceptable ranges of the target values ( $\pm 10$  mmHg for AP,  $\pm 10$   $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  for CO,  $\pm 2$  mmHg for Pla), and the standard deviations of the steady-state differences between AP and AP\*, between CO and CO\*, and between Pla and Pla\*. Because steady states were reached within 30 min in all the variables in the present study, standard deviations were calculated from 30 min after the loop was closed.

#### Statistics

Group data are expressed as means (SD) unless otherwise stated. Student's paired *t*-test was used to compare hemodynamic data at baseline and after the coronary embolization. One-way ANOVA with Tukey's post hoc test was used to compare hemodynamic data before, during, and after the closed-loop control of hemodynamics. The level of statistical significance was defined as  $P < 0.05$ .

#### RESULTS

Hemodynamic data at baseline and after left circumflex coronary artery embolization are summarized in Table 1. Coronary embolization more than doubled Pla [from 7.5 (SD 1.9) to 19.4 (SD 6.2) mmHg] and halved CO [from 131.4 (SD

Table 1. Hemodynamic data at baseline and after left circumflex coronary artery embolization

	Baseline	Embolization
HR, beats/min	141.3 (19.5) [112.0–188.3]	146.2 (28.8) [81.4–197.9]
AP, mmHg	109.1 (18.7) [76.4–140.0]	90.9 (16.5) [66.9–135.6]*
CO, ml·min <sup>-1</sup> ·kg <sup>-1</sup>	131.4 (40.9) [64.5–229.2]	66.8 (23.3) [30.3–121.7]*
Pla, mmHg	7.5 (1.9) [4.7–12.8]	19.4 (6.2) [7.9–34.5]*
Pra, mmHg	4.2 (1.2) [2.1–7.2]	6.0 (1.8) [3.5–9.9]*
S <sub>L</sub> , ml·min <sup>-1</sup> ·kg <sup>-1</sup>	54.3 (18.1) [25.2–105.9]	19.1 (7.6) [8.0–33.7]*
R, mmHg·min·ml <sup>-1</sup> ·kg	0.9 (0.4) [0.4–1.8]	1.4 (0.5) [0.7–2.6]*
V, ml/kg	31.0 (6.6) [21.7–45.2]	32.3 (4.9) [20.6–43.7]

Values are means (SD) ( $n = 35$  in each group). Numbers in brackets are the ranges. HR, heart rate; AP, systemic arterial pressure; CO, cardiac output; Pla, left atrial pressure; Pra, right atrial pressure; S<sub>L</sub>, pumping ability of the left heart; R, systemic arterial resistance; V, stressed blood volume. \* $P < 0.01$  vs. baseline.

40.9) to 66.8 (SD 23.3) ml·min<sup>-1</sup>·kg<sup>-1</sup>]. This decreased S<sub>L</sub> to about one-third of the baseline value, which indicates substantial downward shift of the left cardiac output curve. These changes are compatible with severe LVF.

#### Response of Cardiovascular Parameters to Drug Infusion

Figure 3 shows the open-loop responses of cardiovascular parameters to drug infusions. Figure 3, A and B, shows the averaged time course of  $\delta S_L$  during Dob infusion ( $n = 10$ )

and that of  $\delta R$  during SNP infusion ( $n = 6$ ), respectively. Dob infusion increased  $\delta S_L$ , and SNP infusion decreased  $\delta R$  exponentially. The results of the fit of  $\delta S_L$  and  $\delta R$  to Eq. 1 are summarized in Table 2. The fact that the correlation coefficients were close to unity, with a small standard error of the estimate relative to the amount of  $\delta S_L$  and  $\delta R$ , suggested that the approximation of  $\delta S_L$  and  $\delta R$  to Eq. 1 was reasonably accurate. On the basis of the averaged parameters of the transfer function (Table 2), we determined the PI gain constants for Dob infusion [ $K_i = 0.01$  s<sup>-1</sup>,  $K_p = 0.06$   $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (ml·min<sup>-1</sup>·kg<sup>-1</sup>)<sup>-1</sup>] and for SNP infusion [ $K_i = 0.007$  s<sup>-1</sup>,  $K_p = -1.37$   $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (mmHg·min·ml<sup>-1</sup>·kg)<sup>-1</sup>].

Figure 3C shows the averaged time course of  $\delta V$  in response to Dex infusion ( $n = 5$ ).  $\delta V$  increased and plateaued [7.2 ml/kg (SD 2.2)] after the cessation of Dex infusion.  $\delta V$  at the plateau was greater than the total volume of Dex infused (4 ml/kg), suggesting transvascular fluid absorption by colloid osmotic pressure (3). Figure 3D shows the averaged time course of  $\delta V$  after a single intravenous injection of Fur (20 mg,  $n = 7$ ).  $\delta V$  gradually decreased and reached a trough [-4.3 ml/kg (SD 3.5)] around 30 min after the Fur injection. Average urine volume was 180 ml (SD 94). On the basis of these responses, we determined the constants of the if-then rules as  $X_1 = 1$  ml/kg,  $Y_1 = 10$  ml/min,  $X_2 = -2$  ml/kg, and  $Y_2 = 10$  mg. To avoid oscillation between hypovole-

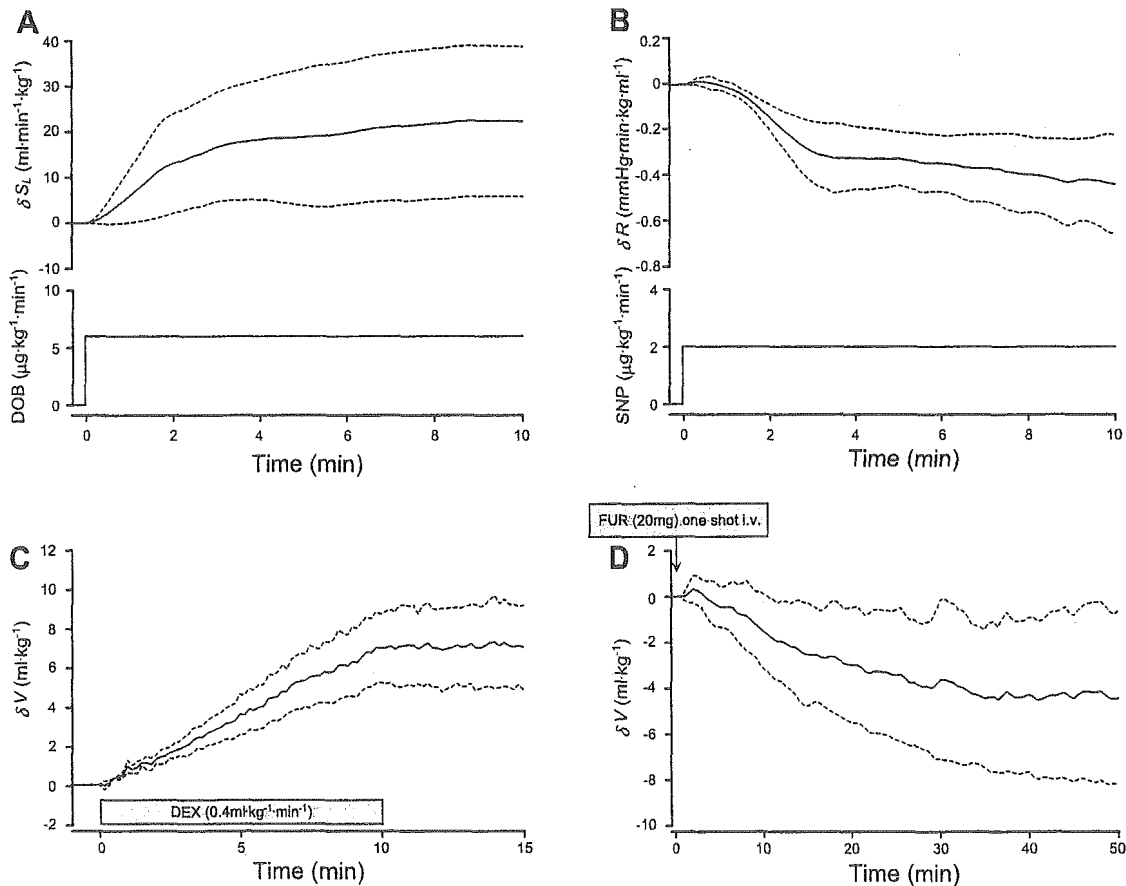


Fig. 3. Response of cardiovascular parameter to drug infusion. A: averaged response of S<sub>L</sub> to stepwise Dob infusion (6  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) ( $n = 10$ ). The ordinate indicates change in S<sub>L</sub> from baseline ( $\delta S_L$ ). B: averaged response of R to stepwise SNP infusion (2  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) ( $n = 6$ ). The ordinate indicates change in R from baseline ( $\delta R$ ). C and D: averaged response of V to Dex infusion (0.4 ml·min<sup>-1</sup>·kg<sup>-1</sup>) (C,  $n = 5$ ) and to Fur (20 mg) injection (D,  $n = 7$ ). The ordinates indicate change in V from baseline ( $\delta V$ ). Data are expressed by mean (solid line)  $\pm$  SD (broken line).

Table 2. Parameters of step response of  $S_L$  and  $R$ 

	$G$	$L$	$T$	$r$	SEE
$\delta S_L$	3.6 (2.7)	63.5 (46.9)	79.0 (78.0)	0.91 (0.09)	2.0 (0.7)
$\delta R$	-0.21 (0.08)	69.8 (26.1)	117.1 (80.2)	0.93 (0.02)	0.06 (0.02)

Values are means (SD).  $\delta S_L$ , change in  $S_L$  from baseline;  $\delta R$ , change in  $R$  from baseline;  $G$ , static gain of  $\delta S_L$  [ $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) $^{-1}$ ] and of  $\delta R$  [ $\text{mmHg}\cdot\text{min}\cdot\text{ml}^{-1}\cdot\text{kg}$  ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) $^{-1}$ ];  $L$ , transport delay (s);  $T$ , time constant (s);  $r$ , correlation coefficient; SEE, standard error of the estimate of  $\delta S_L$  ( $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ) and of  $\delta R$  ( $\text{mmHg}\cdot\text{min}\cdot\text{ml}^{-1}\cdot\text{kg}$ ).

mia and hypervolemia (hence infusion of Dex and injection of Fur), we introduced a dead zone ( $-2 \text{ ml/kg} < \Delta V < 1 \text{ ml/kg}$ ) into the rules (4). We set continuous checking for *rule 1* and checking at 20-min intervals for *rule 2*.

With the controllers thus designed, we evaluated the performance of the automated system in the next protocol.

#### Performance of the Automated Drug Delivery System

Figure 4 shows the experimental trial in a representative case. The automated system was activated at 0 min. Figure 4A 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 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 cardiovascular parameters, the automated system controlled AP, CO, and Pla accurately and stably as demonstrated in Fig. 4C. AP, CO, and Pla reached their respective target levels within 30 min and remained at these levels.

Figure 5 summarizes the results obtained for 12 dogs (*group I*), demonstrating the effectiveness of the performance of the automated system. Figure 5A shows averaged time courses of

the infusion rates of Dob and SNP, and the accumulated volume of infused Dex. The average infusion rates of Dob and SNP were  $4.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (SD 2.6) and  $4.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (SD 1.8), respectively. The average volume of infused Dex was  $2.4 \text{ ml/kg}$  (SD 1.9). Fur was injected once in one animal and twice in another animal. In these two animals,  $V$  decreased by  $3.8$ – $10.2 \text{ ml/kg}$  in response to the injection of Fur with a total urine volume of  $250$ – $300 \text{ ml}$ . Figure 5B shows averaged time courses of difference between  $S_L$  and  $S_L^*$  ( $S_L - S_L^*$ ), difference between  $R$  and  $R^*$  ( $R - R^*$ ), and difference between  $V$  and  $V^*$  ( $V - V^*$ ). Once the system was activated, these differences rapidly converged to the zero lines in all the animals.  $S_L$  was restored to subnormal conditions [ $33.0 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  (SD 2.6)] irrespective of the magnitude of depression before the control [ $13.8 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  (SD 3.5), from  $9.4$  to  $20.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ]. These resulted in accurate and stable control of AP, CO, and Pla (Fig. 5C). The ordinates of Fig. 5C indicate the difference between AP and AP\* ( $AP - AP^*$ ), difference between CO and CO\* ( $CO - CO^*$ ), and difference between Pla and Pla\* ( $Pla - Pla^*$ ). These differences also converged to the zero lines rapidly. The average times for AP, CO, and Pla to reach the acceptable ranges were  $5.2 \text{ min}$  (SD 6.6),  $6.8 \text{ min}$  (SD 4.6), and  $11.7 \text{ min}$  (SD 9.8),

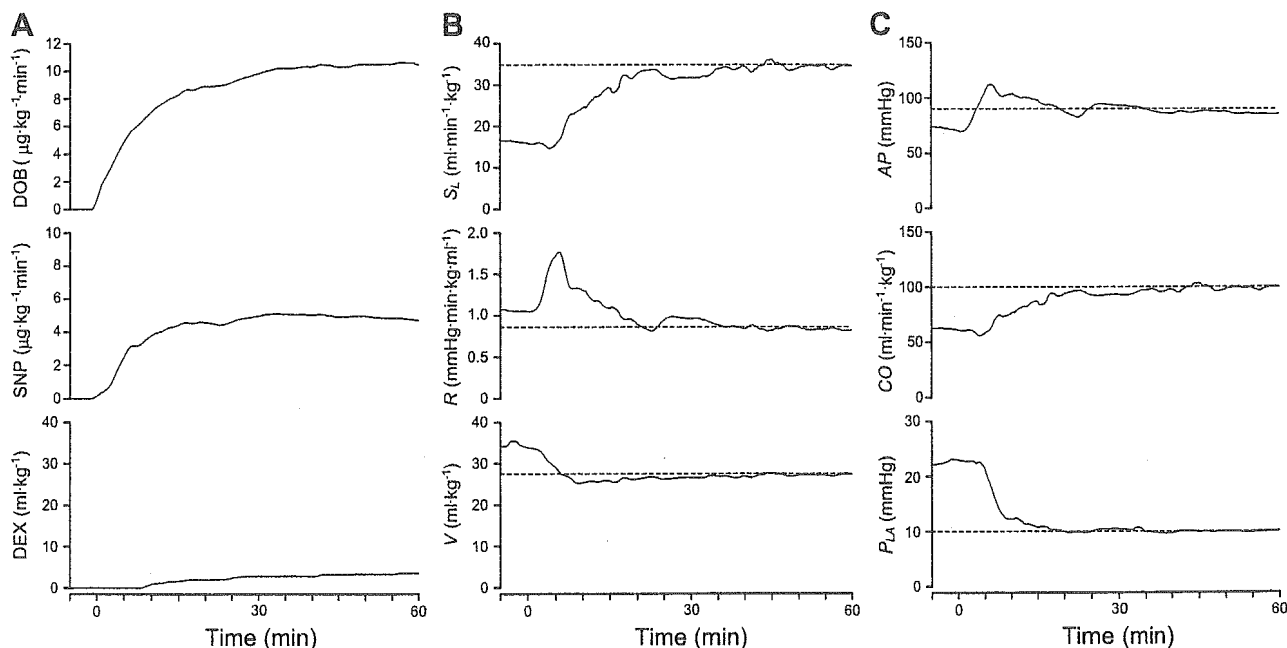


Fig. 4. Time courses of infusion rates of Dob and SNP, and cumulated volume of infused Dex (A), cardiovascular parameters (B), and hemodynamic variables (C) in 1 representative animal during closed-loop control of hemodynamics. Broken horizontal lines in B indicate target parameters (top,  $S_L^*$ ; middle,  $R^*$ ; bottom,  $V^*$ ). Broken horizontal lines in C indicate target hemodynamic variables (top,  $AP^*$ ; middle,  $CO^*$ ; bottom,  $Pla^*$ ). Drug infusion rates were adjusted so that the cardiovascular parameters reached the respective target values. As the parameters got closer to their targets, all 3 hemodynamic variables approached their respective target values.