H20年度厚生労働科学研究費補助金（医療機器開発推進研究事業）
分担研究報告書

循環器病治療機器の医工連携による研究開発・製品化・汎用化を実現するための基盤整備に関する研究

臨床研究・治験に関する基盤整備：データマネジメント体制構築に関する研究

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研究要旨

臨床研究において、治療法等の有効性と安全性に関する情報を正しく把握し、エビデンスを確立していくために、臨床研究の品質管理が重要である。そこで、臨床研究の品質管理を効率的に進めるために、症例報告書とデータベースを一体化し、研究の計画から終了までをサポートする臨床データ管理システムの開発および検証を進めるとともに、具体的な研究課題に対してデータマネジメント支援を実施した。

A. 研究目的

国立循環器病センターは生活習慣病を専門とする唯一のナショナルセンターであり、医薬品のみならず、侵襲性の高い医療機器の治験の経験も多い。また、多施設共同で行う臨床研究の実施件数も多い。研究所で開発された先進医療技術を活用したトランスレーショナルリサーチや治験推進研究事業による医師主導治験を実施している実績を有する。さらに2007年度より「次期治験活性化五カ年計画」の中核病院に選定され、治験及び自主臨床研究の推進を担い、自主臨床研究の支援体制を構築するため、データマネジメント体制の構築を目指した

B. 研究方法

院内で実施される研究課題において各研究に適切なデータマネジメント体制を構築するため、計画段階からデータマネージャーが支援を行い、データマネジメント計画を作成し、運用する。また、初心者を対象としたデータマネージメント実習を実施する。

（倫理面への配慮）

疫学研究に関する倫理指針、臨床研究に関する倫理指針またはヒトゲノム・遺伝子解析研究に関する倫理指針にのっとり計画された研究で、倫理委員会の承認を受けた上で行われる臨床研究を扱う。

C. 研究結果

臨床研究センターで募集・選定した支援課題において、研究ごとにふさわしいデータマネジメントの方法を検討し、データマネジメントシステムの運用も図りながら、データマネジメントを進めた。各支援研究での進捗を記載した。具体的には、各研究の症例データ管理システムの設計、症例報告書の作成、データマネジメント計画書の作成、症例登録方法の設定等と、実際の運用を行った。

また、多施設共同研究において、いくつかの研究では、データマネージャーが他施設の研究者等に対してデータマネジメントシステムの説明・指導を行った。

臨床研究におけるデータマネジメントの必要性や実際について、一般に広く知られていないため、データマネジメント初心者や、データマネジメントに興味のある院内研究者等を対象に、データマネジメント実習を年に2回の頻度で行った。

実習の内容はデータマネジメントの必要性、研究プロトコルの説明、データベース定義書、症例報告書の作成、データクリーニング等である。

D. 考察

複数の具体的な臨床研究において、データ管理システムのみならず、症例報告書や研究実施者側に近い部分での品質管理を含めて検討を行った。特に、研究の計画段階で、研究者とともにデータマネジメントについて具体的に相談し、評価項目、スケジュールなどを作成していくことが、研究全体に対してより効率的であることがわかった。今後、データマネジメント体制の標準化を進めることが、データセンター機能の効率化、複数の研究の比較検討性の向上、各研究のデータの品質向上につながると考える。

E. 結論

具体的な研究においてデータマネジメントを展開し、今後多数の研究に展開ができるような方策を検討した。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

なし

H. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

なし

2. 実用新案登録

なし

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ORIGINAL ARTICLE

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Development of a compact wearable pneumatic drive unit for a ventricular assist device

Abstract The purpose of this study was to develop a compact wearable pneumatic drive unit for a ventricular assist device (VAD). This newly developed drive unit, 20 × 8.5 × 20 cm in size and weighing approximately 1.8 kg, consists of a brushless DC motor, noncircular gears, a crankshaft, a cylinder–piston, and air pressure regulation valves. The driving air pressure is generated by the reciprocating motion of the piston and is controlled by the air pressure regulation valves. The systolic ratio is determined by the noncircular gears, and so is fixed for a given configuration. As a result of an overflow-type mock circulation test, a drive unit with a 44% systolic ratio connected to a Toyobo VAD blood pump with a 70-ml stroke volume achieved a pump output of more than 7 l/min at 100 bpm against a 120 mmHg afterload. Long-term animal tests were also performed using drive units with systolic ratios of 45% and 53% in two Holstein calves weighing 62 kg and 74 kg; the tests were terminated on days 30 and 39, respectively, without any malfunction. The mean aortic pressure, bypass flow, and power consumption for the first calf were maintained at 90 ± 13 mmHg, 3.9 ± 0.9 l/min, and 12 ± 1 W, and those for the second calf were maintained at 88 ± 13 mmHg, 5.0 ± 0.5 l/min, and 16 ± 2 W, respectively. These results indicate that the newly developed drive unit may be used as a wearable pneumatic drive unit for the Toyobo VAD blood pump.

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Key words Wearable pneumatic drive unit · Ventricular assist device · Cylinder–piston · Noncircular gear · Air pressure regulation valve

Introduction

Pneumatic drive units for ventricular assist devices (VADs) currently used in Japan are large (the size of a small refrigerator), heavy (90–240 kg), and have a high power consumption (400–500 W) because a compressor and a vacuum pump are used to generate the air pressure to drive a diaphragm-type blood pump.[1–6] To solve these problems with the external VAD drive units that restrict the flexibility of the patient's everyday life, a portable drive unit (Mobart-NCVC) was developed at our institute.[7–9] By utilizing the air pressure generating mechanism of an electrohydraulic pump, we were able to devise a small (35 × 30 × 45 cm), lightweight (13 kg), low-power (30–50 W) portable pneumatic drive unit. In other research organizations and companies, various console-type and portable drive units have already been developed.[10–24] For example, the TLC-II portable driver (Thoratec, Pleasanton, CA, USA) can be used for univentricular or biventricular support. The size and weight of the TLC driver are 34 × 34 × 14 cm and 7.5–9.8 kg, and rechargeable lithium-ion batteries provide up to 80 min of support. Furthermore, the mobile driving system Excor Mobile (Berlin Heart, Berlin, Germany) can be used for univentricular and biventricular support. The Excor Mobile system is the size of a baby carriage and weighs 9 kg; rechargeable batteries are able to supply the system with electricity for between 5 and 8 h. In addition, this system is used for the CardioWest TAH-t total artificial heart (SynCardia Systems, Tucson, AZ, USA) in Europe. However, carry-type portable drive units weighing as much as 10 kg are still not able to deliver great freedom of movement for patients. To improve the patient's quality of life, it is desired to develop a compact wearable drive unit that enables comfortable adaptation, greater freedom of movement, and longer operation time on batteries. Therefore,

the purpose of this study was to develop a wearable pneumatic drive unit that can drive the Toyobo diaphragm-type VAD blood pump currently used clinically. The specific targets of this study were as follows: (1) a pump output of more than 7 l/min at 100 bpm against an afterload of 120 mmHg; (2) a size equivalent to a shoulder bag that does not restrict the patient's actions; (3) a weight of less than 3 or 4 kg so as not to become a burden on the patient; (4) a low power consumption with more than 2 h of battery operation; and (5) the same operability, durability, and safety levels as those of conventional pneumatic drive units. To achieve these targets, an air pressure generating mechanism using a cylinder–piston was developed. This article describes the results of performance evaluation and long-term animal tests for the prototype wearable pneumatic drive unit.

Material and methods

Description of the wearable pneumatic drive unit

The newly developed drive unit consists of a brushless DC motor, noncircular gears, a crankshaft, a cylinder–piston, and air pressure regulation valves (Fig. 1). A photograph of the drive unit is given in Fig. 2. The size of the unit is 20 × 8.5 × 20 cm and it weighs approximately 1.8 kg. The main material of the drive unit, apart from the motor, is aluminum (AL5056), and the noncircular gears are made of hot-rolled steel plate (PH40). Air pressure is generated by the reciprocating movement of the piston. A sealing technique using fluorocarbon resin has been applied to the sliding surface of the cylinder–piston. This fluorocarbon resin seal does not require any lubricating oil and prevents oil mist generation in the blood pump air chamber. The cylinder–piston has a volume of 90 ml in consideration of the 70-ml stroke volume of the Toyobo blood pump and the 2 m length and 6 mm internal diameter of the air hose. The crankshaft converts the rotational movement of the brushless DC motor to the reciprocating movement of the piston. Because the rotational speed during the pulsation cycle can be changed by the noncircular gears located between the motor shaft and the crankshaft (Fig. 3), the systolic ratio is fixed at a set value by adjusting the gears beforehand. For this study, several systolic ratios have been made available by using drive units with different gears. The function of maintaining the filling and ejecting state of the blood pump has been omitted from the drive unit. Maximum and minimum driving air pressure values are limited by the air pressure regulation valves, which consist of springs and a diaphragm. Rotation-type knobs adjust the expansion and contraction of the springs that control the opening and closing behavior of the valve. By use of this mechanism without a complicated electronic control system, driving air pressure is always maintained within a set range, and the air volume in the cylinder is properly regulated. This regulation mechanism also functions quickly after the connection of the air hose when the blood pump or the drive unit is exchanged.

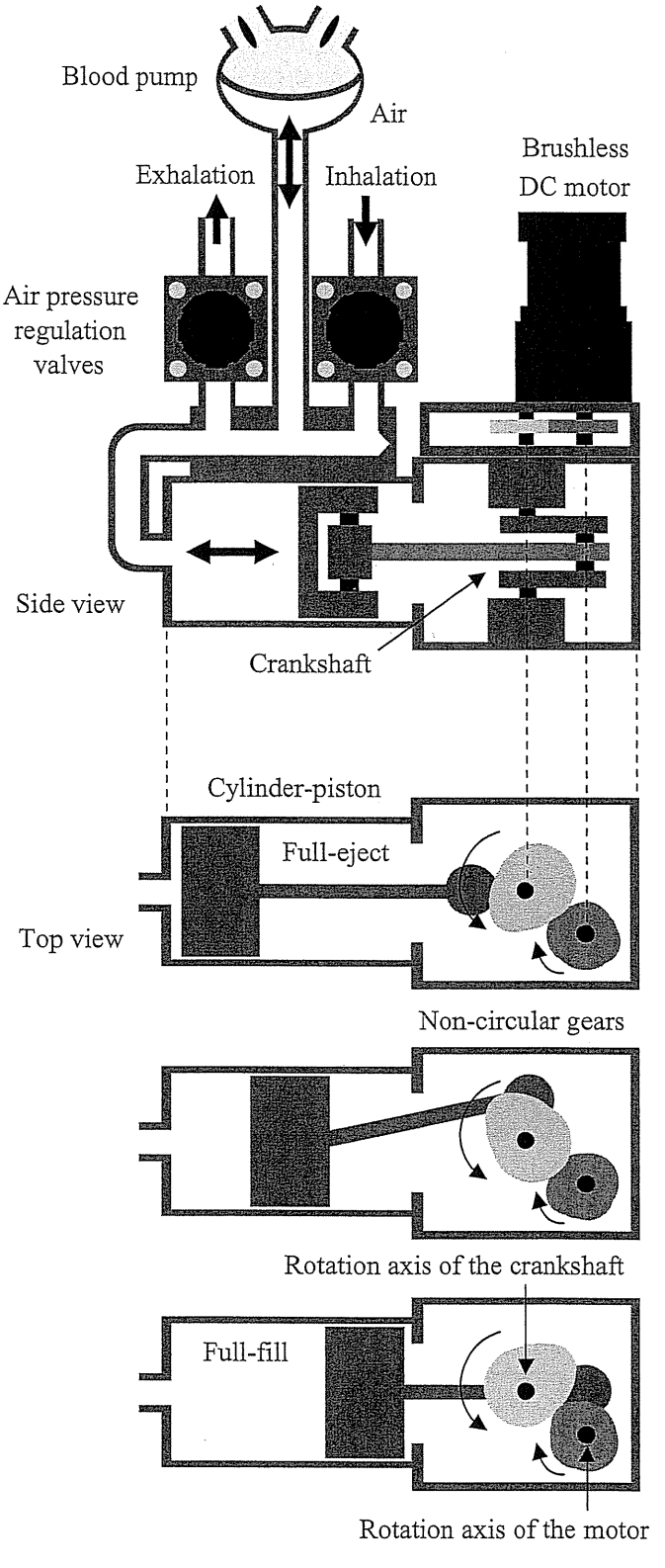

Fig. 1. Mechanism of the drive unit

Performance evaluation using an overflow-type mock circulation test

The performance of the drive unit was evaluated using an overflow-type mock circulation test. A Toyobo VAD blood

pump with a 70-ml stroke volume was connected to the drive unit using a 2-m air hose. The preload at the inlet port of the blood pump was set at 10 mmHg, and the afterload at the outlet port of the blood pump was set at three different pressures: 80, 100, and 120 mmHg. The lengths of the inlet and outlet cannulas were 20 cm and 30 cm, respectively, and the internal diameters were14 mm. Tap water was used as the circulation fluid in the mock circulation, and the pump output was measured using an ultrasonic flow meter (T106, Transonic Systems, New York, NY, USA) attached to the outlet cannula. The ultrasonic flow meter was calibrated according to preliminary tests. The blood pump was regulated in full-fill and full-eject conditions at 10 bpm intervals from 60 to 100 bpm using a systolic ratio of 44%. The full-fill and full-eject conditions were adjusted by means of the measured pump stroke volume and visual evaluation of the pump diaphragm.

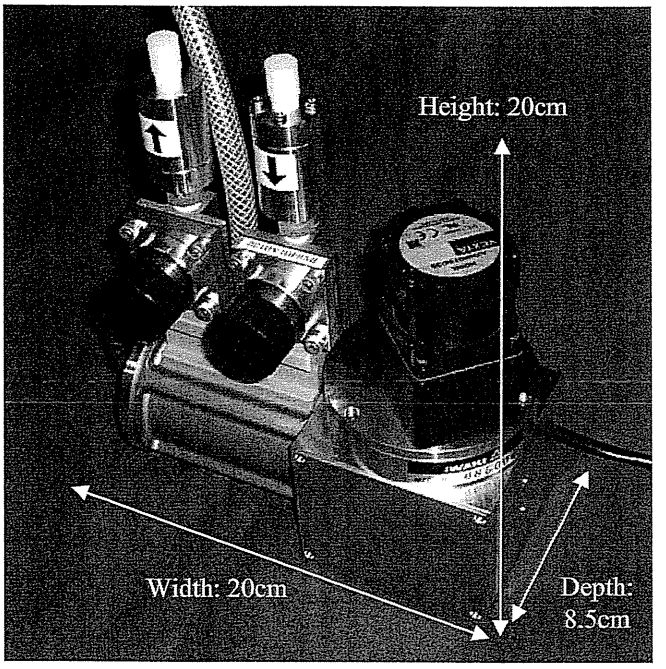

Fig. 2. Photograph of the drive unit

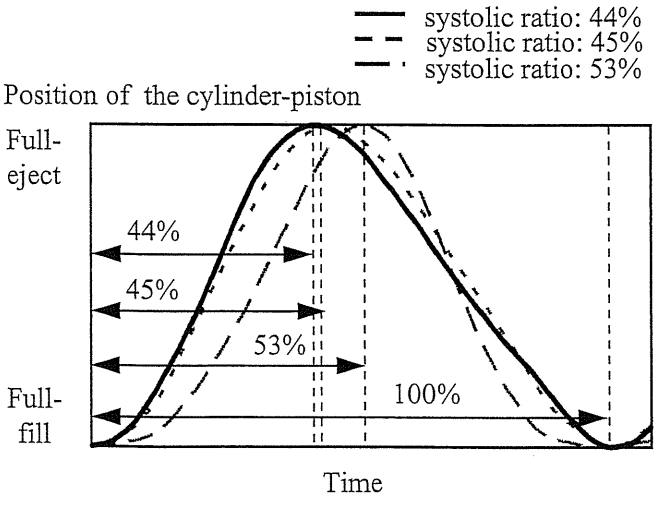

Fig. 3. Piston position profiles for three different systolic ratios

Animal preparation

Long-term animal tests were performed using two Holstein calves weighing 62 and 74 kg. They underwent a left heart bypass, and a Toyobo VAD blood pump with a 70-ml stroke volume was implanted. The inflow cannula was connected to the left ventricular apex, and the outflow cannula was led to the ascending aorta. The calves wore the drive unit on their backs, and the blood pump was attached to the left chest wall using a 2-m air hose. The lengths of the inlet and outlet cannulas were 50 cm and 40 cm, respectively, and the internal diameter was 14 mm. After the surgical operation, the blood pump was first driven using the Toyobo VAD console-type pneumatic drive unit. Stability was achieved after the first postoperative week or more, and the Toyobo drive unit was exchanged for the newly developed pneumatic drive unit. The systolic ratio of the drive unit was selected according to the blood circulation of the calves to maintain sufficient bypass flow and adequate driving conditions of the blood pump.

Institutional guidelines for the care and use of laboratory animals were observed. All protocols were reviewed and approved by the Animal Subjects Committee of the National Cardiovascular Center.

Battery test procedures

The battery operation time of the drive unit was examined in both the overflow-type mock circulation test and the animal tests. Three types of commercially available lithium-ion rechargeable batteries were used. A photograph of the batteries and the specifications of the batteries are given in Fig. 4 and Table 1, respectively. Because each battery had

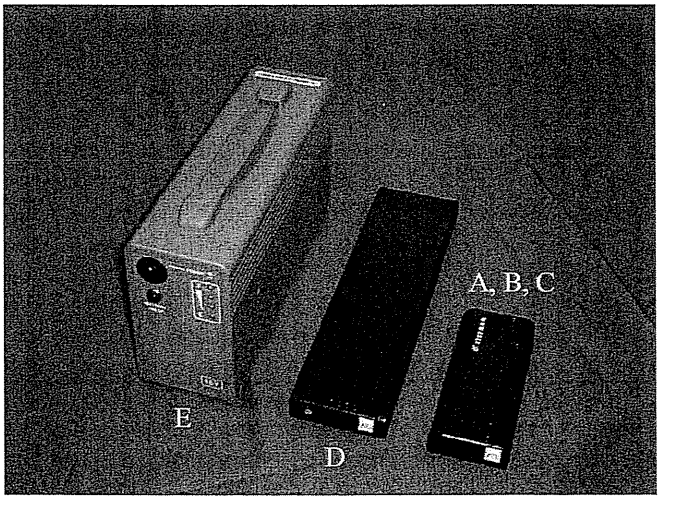

Fig. 4. The batteries used in the experiments. Details are given in Table 1

Table 1. Specifications of the batteries

	Battery type		
	A, B, C	D	E
Weight (g)	250	720	2800
Size (W × D × H) (mm)	140 × 60 × 23	280 × 75 × 23	80 × 260 × 140
Output voltage (V)	14.4	22.2	16.0
Service capacity (Wh)	30	89	213

A DC-DC converter was used to convert the different output voltages of the batteries to the 24-V input voltage of the drive unit

Table 2. Summary of the animal tests

	Calf 1	Calf 2
Body weight (kg)	62	74
Duration (days)	30	39
Mean aortic pressure (mmHg)	90 ± 13	88 ± 13
Mean bypass flow (l/min)	3.9 ± 0.9	5.0 ± 0.5
Beating rate (bpm)	80	55 – 70
Systolic ratio (%)	53	45, 53
Mean power consumption (W)	12 ± 1	16 ± 2
Event	None	Infection of the inlet cannula

In the second calf, two different drive units with systolic ratios of 45% and 53% were evaluated

a different output voltage, a DC–DC converter was used to convert the different output voltages to the 24-V input voltage of the drive unit.

Results

Performance evaluation test

The flow rate characteristics of the drive unit in the overflow-type mock circulation test are shown in Fig. 5. The flow rates of the blood pump increased linearly with increases in the beating rate. The pump output was slightly less than expected at 100 bpm with an afterload of 120 mmHg. However, more than 7 l/min of pump output was obtained at 100 bpm for all afterloads (80, 100, and 120 mmHg). The average power consumption varied from 8.6 to 17.7 W according to the beating rate and afterload. The dynamic stroke volume of the blood pump, which was calculated at all measured points, ranged from 63 to 77 ml. Because the static stroke volume of the Toyobo blood pump was approximately 70 ml, the driving conditions of the blood pump were maintained in the full-fill and full-eject conditions. Although the systolic ratio of this drive unit was fixed at 44%, the driving conditions were controlled at full-fill and full-eject conditions by regulating the beating rate and the driving air pressure.

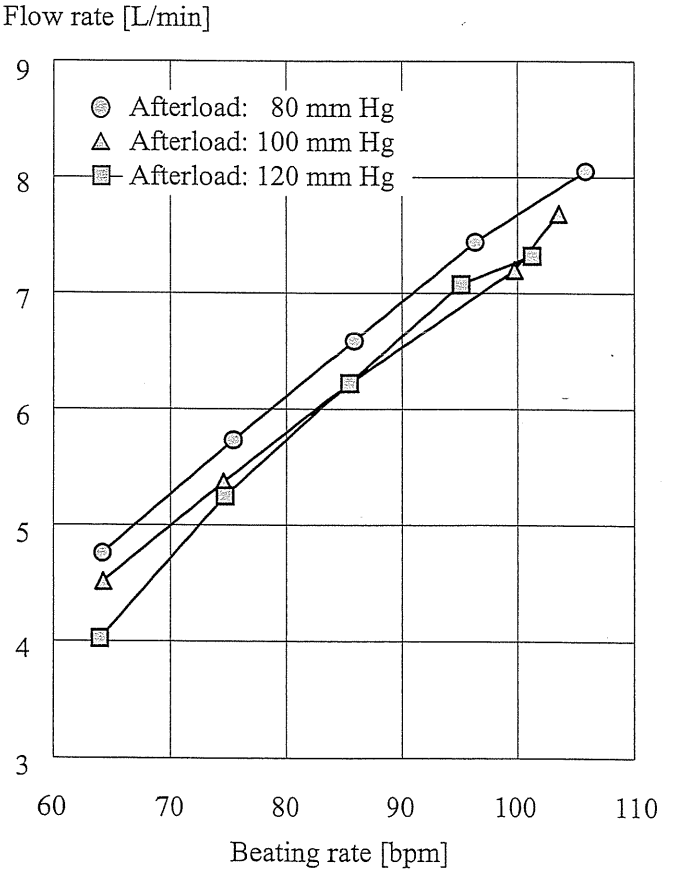

Fig. 5. Flow rate of the Toyobo blood pump connected to the test drive unit in an overflow-type mock circulation system

Long-term animal tests

Long-term animal tests were performed as shown in Fig. 6. After the surgical operation, the blood pump was first driven using the Toyobo drive unit for at least 1 week. Once stability had been established, the Toyobo drive unit was exchanged for the wearable pneumatic drive unit without any problems. After the exchange of the drive unit, small changes in the beating rate and driving air pressure were observed, but a significant drop in the pump output did not occur. A summary of the long-term animal tests is given in Table 2. The first experiment was terminated on schedule

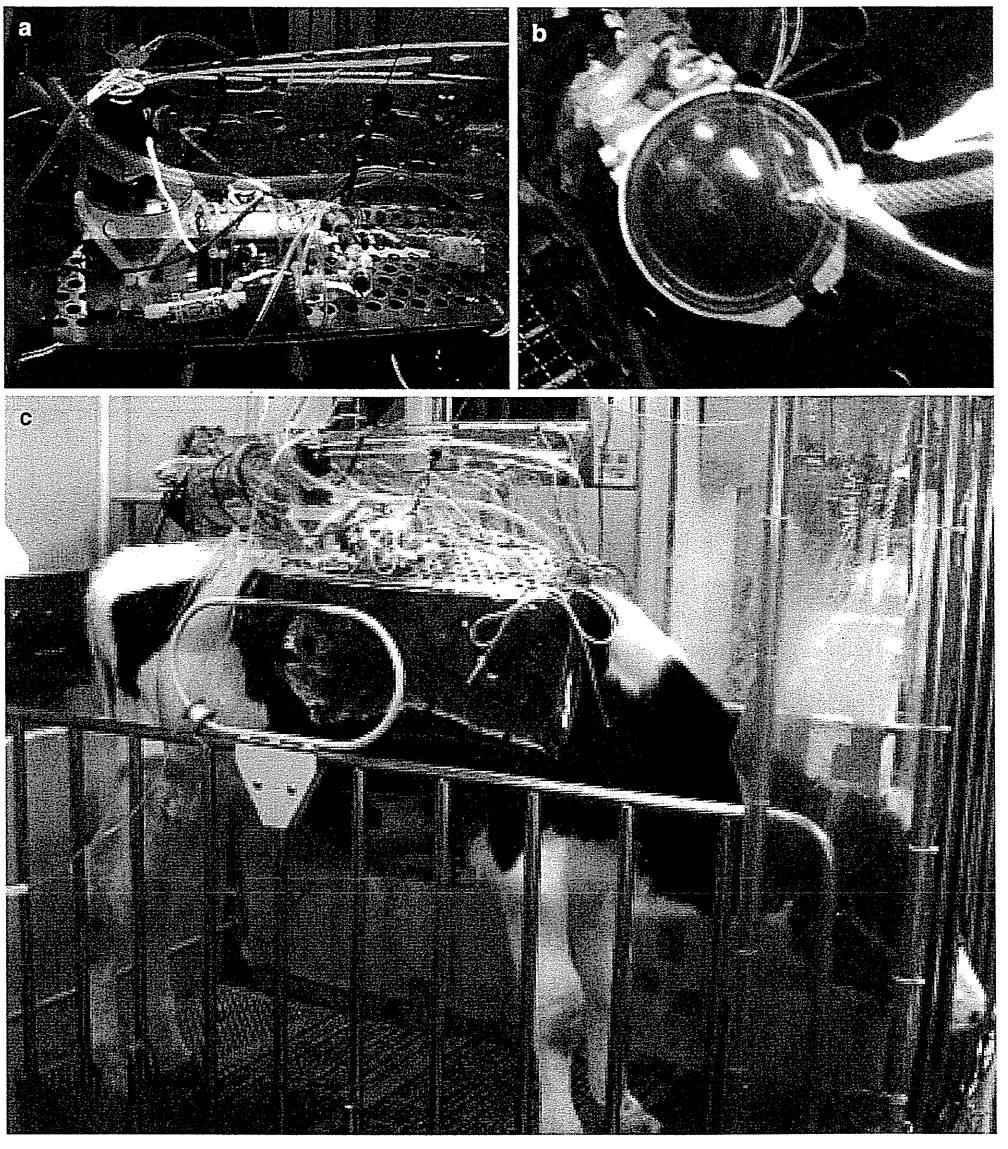

Fig. 6a–c. Long-term animal test of the drive unit: **a** the drive unit, **b** the Toyobo blood pump, and **c** the Holstein calf undergoing the long-term animal test

after 30 days without any adverse events. The second experiment was terminated on postoperative day 39 because of a rapid decrease in the bypass flow, which resulted from thrombosis and granulation formation on the tip of the inlet cannula. The thrombosis formation was caused by an infection at the skin cuff of the inlet cannula, and the granulation formation was caused by the fitting of the inlet cannula. However, the drive unit ran continuously for 39 days without any malfunction.

In both cases, the calves remained in good general condition until the termination of the experiments. Figure 7 shows the changes in the mean aortic pressure, the bypass flow, and the power consumption for the second calf. The beating rate was set from 55 to 70 bpm, and the mean power consumption of the drive unit was maintained at 16 ± 2 W. The mean aortic pressure and bypass flow were maintained at 88 ± 13 mmHg and 5.0 ± 0.5 l/min, respectively. Figure 8 shows the changes in the biochemistry data for the second calf. Neither renal insufficiency nor hepatic insufficiency was recognized during the experiment. Anticoagulation therapy was performed by oral administration of warfarin potassium and aspirin. The prothrombin time before the operation was used as the index of anticoagulant control.

In the second calf, a rapid decrease in the flow of the left heart bypass was recognized during the last three days, before termination of the experiment. In this case, the driving condition of the blood pump and the pump output could not be controlled by regulation of the beating rate and the driving air pressure only. The Toyobo drive unit with a systolic ratio of 15% improved the filling and ejecting conditions of the blood pump, but did not improve the pump output. Some differences in the regulation performance between the conventional drive unit and the newly developed drive unit with fixed systolic ratios of 45% and 53% were confirmed.

Waveforms of the aortic pressure, bypass flow, and driving air pressure for the second calf are shown in Fig. 9. The driving air pressure waveair pressure waveforms of the

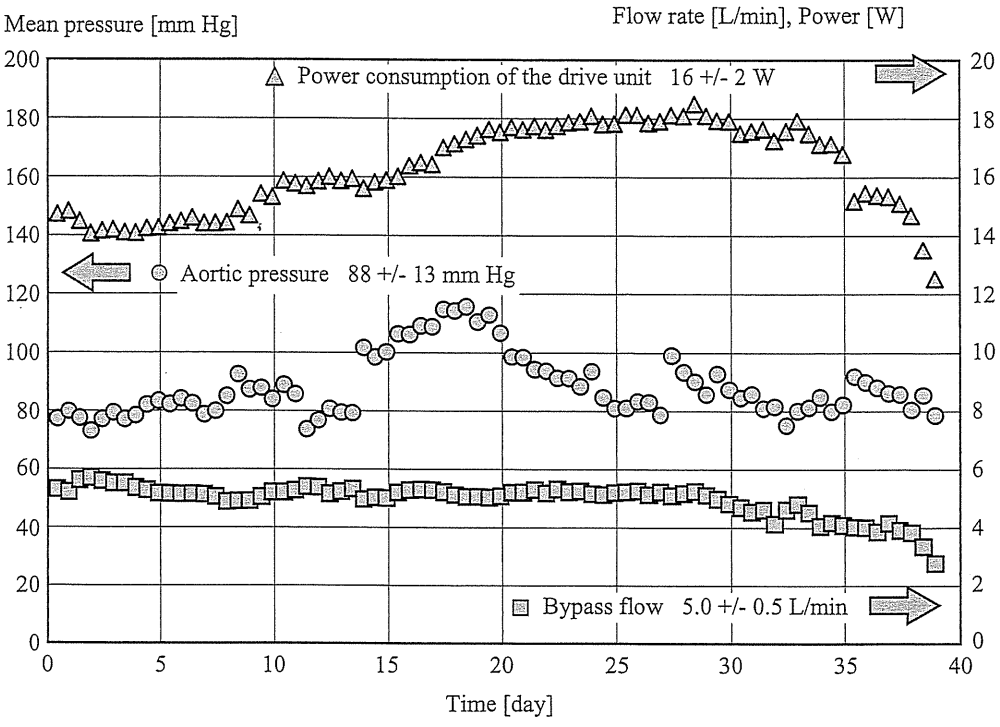

Fig. 7. Changes in mean aortic pressure, bypass flow, and power consumption during a long-term animal test

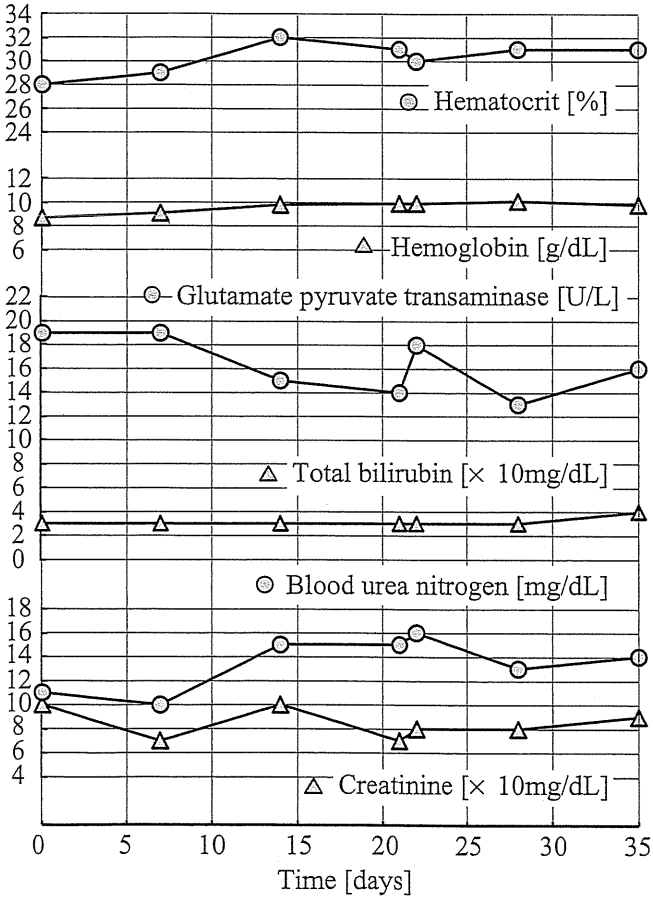

Fig. 8. Hematocrit, hemoglobin, glutamate pyruvate transaminase, total bilirubin, blood urea nitrogen, and creatinine levels over the course of the animal experiment

wearable pneumatic drive unit differed from those of the conventional pneumatic drive unit. The driving air pressure waveforms of the conventional drive unit were rectangular, but those of the wearable drive unit were more sinusoidal. Compared with the conventional drive unit, large set values of the maximum and minimum driving air pressure were needed for the newly developed drive unit to achieve the same pump output.

Battery tests

The results of the battery tests are summarized in Tables 3 and 4. The small, medium, and large batteries (250, 720, and 2800 g) demonstrated a battery operation time of more than 80 min, 4 h, and 13 h, respectively. The beating rate was set at 80 bpm and the mean bypass flow was maintained at approximately 4 l/min. Mean power consumption varied from 16.5 to 18.4 W according to the pump pressure head.

Discussion

Flow rate performance

The newly developed drive unit demonstrated a flow rate performance equivalent to that of the conventional drive unit. A blood pump output of more than 7 l/min at 100 bpm was achieved in the overflow-type mock circulation test. Furthermore, the new drive unit successfully performed a stable mechanical circulatory support of about 5 l/min for 39 days in the long-term animal test.

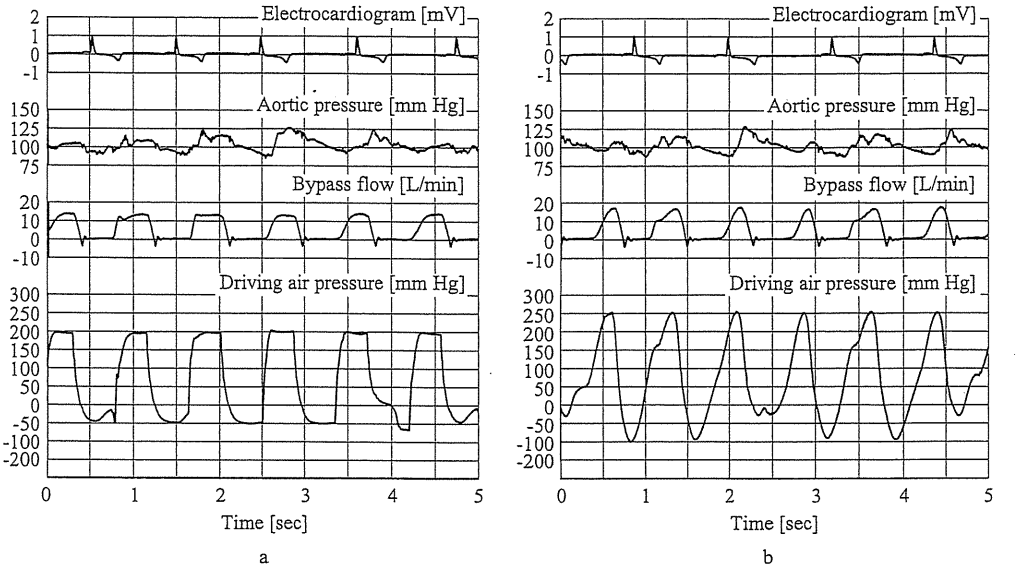

Fig. 9. Electrocardiogram, aortic pressure, bypass flow, and driving air pressure of ventricular unloading for **a** the Toyobo drive unit and **b** the newly developed drive unit.

Table 3. Summary of battery tests in an overflow-type mock circulation

	Battery type				
	A	B	C	D	E
Preload (mmHg)	10	10	10	10	10
Afterload (mmHg)	100	100	100	100	100
Mean flow rate (l/min)	4.0	4.0	4.0	4.0	4.0
Mean power consumption (W)	16.5	16.6	16.8	17.2	17.3
Running time (h)	1:36	1:28	1:26	4:57	14:00

The beating rate and systolic ratio were set at 80 bpm and 45%, respectively

Table 4. Summary of battery tests in animals

	Battery type				
	A	B	C	D	E
Mean left ventricle pressure (mmHg)	50.5	52.3	51.8	48.4	37.6
Mean aortic pressure (mmHg)	88.6	91.2	90.2	87.5	92.4
Mean bypass flow (l/min)	4.2	4.3	4.1	4.2	4.0
Mean power consumption (W)	18.4	17.8	17.4	17.8	18.2
Running time (h)	1:25	1:20	1:19	4:46	13:14

The beating rate and systolic ratio were set at 80 bpm and 45%, respectively
The driving condition of the blood pump was regulated to maintain a mean bypass flow of approximately 4 l/min

Size and weight

The core drive unit was minimized for use as a wearable drive unit for the Toyobo VAD blood pump. The size (20 × 8.5 × 20 cm) and weight (1.8 kg) of the core unit are acceptable for building into a wearable drive unit. However, the batteries, electric circuits, and outer casing are not yet included in this size and weight. In future studies, it will be necessary to realize a target size as small as a shoulder bag and a weight of less than 3 or 4 kg including these component parts.

Carrying methods

How a patient wears and carries the drive unit is very important. It is thought that a backpack type is desirable to facilitate the activities of daily living because the patient is able to use both hands and the load of the drive unit is distributed over the body. In addition, a shoulder bag type is useful for long-distance transport by train or airplane or for prolonged desk work because it can be taken off and placed beside a seat or a desk. It is desirable that the carrying method of the drive unit, i.e., backpack type, shoulder bag type, or carry type, can be chosen according to a patient's preferences and lifestyle. The opinions of medical professionals should also be reflected.

Power consumption and batteries

The overflow-type mock circulation test and long-term animal tests showed that the power consumption of the newly developed drive unit was considerably lower than

that of the conventional drive unit at about 18 W maximum. The battery operation time was dependent on the selection of the battery, which is still under consideration. However, it was confirmed that two commercially available lithium-ion batteries (single unit: 14 × 6 × 2.3 cm, 250 g) would enable a running time of more than 2 h 30 min. The wearable drive unit must be mainly driven by batteries for the greater part of the patient's activities. The specification and selection of the battery should be determined in consideration of the patient's lifestyle.

Operability

The regulation of performance of the new drive unit was different from that of the conventional drive unit. This is because the systolic ratio of the newly developed drive unit was fixed beforehand at 45% or 53% by adjusting the non-circular gears. However, driving parameters are infrequently changed significantly under stable conditions in clinical practice, and the systolic ratio is changed slightly according to the patient's condition. Under stable conditions, it is possible to regulate the driving conditions of the blood pump by using only the beating rate and the driving air pressure. Nevertheless, the long-term animal tests confirmed that the fixed systolic ratio affected the regulation performance of the blood pump driving conditions. In such cases, it is very difficult to maintain the pump output even when using the conventional drive unit because of the disturbance of the blood circulation on the left heart bypass. Some medical intervention is thus required instead of further regulation of the drive unit. Moreover, it is possible to adjust the systolic ratio beforehand so that it corresponds to the patient's condition.

Durability and safety

The new drive unit has advantages with respect to durability and reliability because the drive unit consists of a very simple mechanism without a complicated electrical system. Furthermore, the long-term animal test demonstrated stable mechanical circulatory support for 39 days without any malfunction. However, the driving air pressure waveforms of the newly developed drive unit differed from those of the conventional pneumatic drive unit, and an increase in the maximum and minimum driving air pressure was needed to achieve the same pump output as the conventional drive unit. These differences result from the mechanism generating the driving air pressure. The driving air pressure of the newly developed drive unit is generated continuously during the compression and suction processes of the reciprocating movement of the piston. In contrast, the driving air pressure of the conventional drive unit is generated by switching the positive and negative air pressure accumulated by the compressor and vacuum pump. As a result, the driving air pressure waveforms of the conventional drive unit are rectangular and those of the wearable drive unit were more sinusoidal. The driving air pressure waveforms are directly linked to the motion of the diaphragm. In a further study, the influence of the driving air pressure waveforms on durability must be confirmed by means of a long-term the durability of the blood pumb test in a mock circulation.

Furthermore, it is necessary to monitor and alarm the minimum pump output, the battery residual quantity, and motor malfunction for safe operation. It is also required to estimate the margin of safe running times until maintenance is required or consumable parts are exchanged.

Thrombus formation and hemolysis

The driving air pressure waveforms are directly linked to the motion of the diaphragm, while the diaphragm motion is closely related to the flow behavior inside the blood pump. The flow behavior that may affect thrombus formation has been studied in our institute. The flow velocity distribution in each area of the blood pump was investigated by means of the particle image velocimetry (PIV) visualization method.[25] The mount angles of the inlet and outlet mechanical valves significantly affected the flow behavior inside the blood pump. It is thought that areas of blood flow stagnation coincide with the areas in which thrombus formation frequently occurs. Similarly, if the motion of the diaphragm produces stagnation of flow inside the blood pump, this will influence thrombus formation greatly.

In addition, the cavitation generated on the opening and closing motions of the mechanical valve causes erosion of the valve surface and the hemolysis of blood. The generation mechanism of cavitation has been also studied in our institute. The mechanism varied with the valve closure motions, which depend on the mount angles, the closing time, and the rebound motion of the valve.[26] It is thought that these factors are influenced also by the driving air pressure waveforms. However, it is not yet clear whether the driving air pressure waveforms affect the thrombus formation or hemolysis in the blood pump. In a further study, these mechanisms must be confirmed.

Performance limitations

The newly developed drive unit has some performance limitations because of its very simple mechanism. The systolic ratio of the drive unit is fixed at a set value beforehand. The maximum and minimum driving air pressure values that can be generated by the movement of the piston are limited, and the driving air pressure waveforms are sinusoidal. The blood pump volume and the air hose length are also limited by the volume of the air cylinder. Furthermore, the drive unit does not have the function to maintain the filling and ejecting state of the blood pump. These limitations are necessary to realize its small size, light weight, and low power consumption. However, the final specifications of the drive unit must be sufficiently discussed and decided based on the opinions of medical professionals as well as patients to ensure the safety of the patient.

The price of the drive unit

For the use of a medical device to spread widely, the price of the unit is as important as its performance. A product price will be influenced by not only by the costs of the parts but also by the maintenance expenses of the product supplier and the product supply system. The newly developed drive unit is based on a simple mechanism without a complicated electronic control system. The cost of the newly developed drive unit can thus be held down below that of the conventional drive unit.

Conclusion

We invented an air pressure generating mechanism using a cylinder–piston and successfully developed a prototype wearable pneumatic drive unit. A small size of 20 × 8.5 × 20 cm and a light weight of 1.8 kg were realized, and a blood pump output of more than 7 l/min at 100 bpm against an afterload of 120 mmHg was achieved in an overflow-type mock circulation test. A battery operation time of more than 2 h 30 min was also accomplished using two commercially available lithium-ion batteries weighing 500 g altogether. Moreover, the drive unit successfully performed stable mechanical circulatory support of 5.0 ± 0.5 l/min for 39 days at a low power consumption of 16 ± 2 W in a long-term animal test. The newly developed pneumatic drive unit demonstrated sufficient ability to be used as a compact wearable drive unit for the Toyobo VAD blood pump. This wearable pneumatic drive unit is expected to contribute to the expansion of patients' activities, rehabilitation in society, and the progress of destination therapy.

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ORIGINAL ARTICLE

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Oxygen metabolism during cardiopulmonary bypass with hemodilution using liposome-encapsulated hemoglobin in kid goats

Abstract Cardiopulmonary bypass (CPB) with hemodilution has been proposed as a useful method for many types of cardiovascular surgery. Although the harmful effects of severe hemodilution need to be prevented, blood transfusion should be avoided whenever possible. Therefore, we have been developing a new CPB technique using liposome-encapsulated hemoglobin (LEH). The purpose of this study was to evaluate the combined therapy of diluted CPB and LEH focusing on the influence of LEH on oxygen metabolism. Male kid goats (n = 8) were divided into two groups: the LEH and control groups. CPB was maintained at between 36° and 37°C. There was no significant difference in hemoglobin concentrations (6.3 ± 1.5 g/dl in the LEH group and 6.2 ± 1.3 g/dl in the control group) after initiation of CPB between the two groups. Thus, there was no distinction in oxygen deliveries between the two groups (11.0 ± 2.0 ml/kg/min in the LEH group and 11.0 ± 2.3 ml/kg/min in the control group). Oxygen consumption in the LEH group (2.5–2.7 ml/kg/min), however, had a tendency to be higher than that in the control group (2.4–2.5 ml/kg/min). In addition, the lactate/pyruvate ratio decreased earlier in the LEH group. These results suggest that the application of LEH in the pump-priming solution improves decreased aerobic oxygen metabolism during CPB without any serious adverse effects.

Key words Blood substitute · Artificial oxygen carrier · Liposome-encapsulated hemoglobin · Oxygen consumption · Cardiopulmonary bypass

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Introduction

We have been developing a new artificial oxygen carrier using liposome-encapsulated hemoglobin (LEH) as a blood substitute. Our newly developed LEH has some preferable features for clinical use. First, it has a longer circulation half-time than other artificial oxygen carriers, i.e., between 24 and 30 h.[1] Second, because this LEH is about 200 nm in diameter,[1] which is one-thirtieth the size of a red blood cell, it has the possibility of reaching the peripheral tissues that even red blood cells can barely reach. Third, our LEH may be capable to supply twice as much oxygen to the peripheral tissues as the same volume of hemoglobin in red blood cells because of its controlled oxygen affinity.[2] Finally, although other artificial oxygen carriers induce marked constriction of vessels followed by increased blood pressure, LEH demonstrated only a minor adverse effect on blood pressure.[3,4]

In previous experiments using small animals, it was shown that the efficacy of LEH in the stabilization of hemodynamics was almost the same as that of red blood cells when LEH was infused during blood withdrawal.[5–8] In animals with hemorrhagic shock, LEH was useful even in that condition for resuscitation.[1,9–11] Therefore, this LEH is expected to set as an oxygen carrier without major adverse effects during cardiovascular surgery using cardiopulmonary bypass (CPB) with hemodilution. The purpose of this study was to evaluate the combined therapy of CPB and LEH in large-animal experiments focusing on the influence of LEH on oxygen metabolism.

Materials and methods

Animals

Male kid goats (n = 8) were divided into two groups: a control group (n = 4, body weight 21.5 ± 2.6 kg) and an LEH group (n = 4, body weight 19.8 ± 0.8 kg). The experimental protocol described below met the guidelines for use of

laboratory animals set by the National Cardiovascular Center of Japan.

Liposome-encapsulated hemoglobin (LEH)

In this study, we used LEH prepared at the Terumo Research and Development Center (Terumo, Tokyo, Japan).[1,12] Stroma-free hemoglobin solution obtained from outdated human red blood cells was filtered to remove viruses. After homogeneous hydrated lipids were added to stroma-free hemoglobin with inositol hexaphosphate, the mixture was placed in a high-speed emulsifier to form LEH. Using filtration and ultrafiltration, the LEH suspension was purified and concentrated to 6 g/dl of hemoglobin. Polyethylene glycol covalently bound to hydrogenated phosphatidylethanolamine was added to LEH as a liposomal surface modifier. The average diameter of this LEH was about 200 nm. The partial pressure of oxygen at which 50% of the hemoglobin was saturated (P_{50}) was 45–55 mmHg.

Intervention and cardiopulmonary bypass

Anesthesia was induced and maintained with inhalation of isoflurane throughout the period of the experiments. A temperature probe was placed in the rectum and the tips of saline-filled catheters were located in the aorta and superior vena cava, via the left internal mammary artery and left internal mammary vein, to monitor mean aortic pressure (mAP) and central venous pressure (CVP), respectively.

Following measurement of parameters and the withdrawing of blood samples to establish the pre-CPB condition, the left carotid artery was cannulated with an arterial cannula and the right atrium was cannulated with a two-stage venous cannula. The CPB circuit consisted of a hollow-fiber membrane oxygenator with a hard-shell venous reservoir (Capiox SX10X, Terumo, Tokyo, Japan), a centrifugal pump (Capiox CX-SP4538, Terumo), and an arterial filter (Capiox CX-AF02, Terumo). The 1000 ml of pump-priming solution contained 400 ml of LEH suspension (LEH group) or 400 ml of Ringer's acetate (control group), 520 ml of hydroxyethyl starch, 30 ml of 7% sodium hydrogen carbonate, 50 ml of mannitol, and 2000 U of heparin.

Cardiopulmonary bypass was maintained at between 36° and 37°C, 100–120 ml/kg/min of bypass flow, and 100% fraction of inspiratory oxygen. Oxygen flow was sustained at one-half of the bypass flow. After initiation of CPB, ventricular fibrillation was induced with an electric fibrillator and total CPB was thereby established.

Data collection

The hemodynamic parameters were monitored with a data acquisition system (MacLab/16s, AD Instruments, Castle Hill, Australia). Bypass flow (BF) was measured with a flow meter (T106, Transonic, Ithaca, NY, USA). Oxygen consumption (VO2) before initiation of CPB was determined with an oximeter in the respirator circuit (S/5 Compact Critical Care Monitor, GE Healthcare, Chalfont St. Giles, UK). Blood analysis, including arterial oxygen pressure (PaO2), venous oxygen pressure (PvO2), blood lactate level, hemoglobin concentration (Hb), arterial oxygen saturation (SaO2), and venous oxygen saturation (SvO2), was performed with a blood gas analyzer (ABL, Radiometer, Copenhagen, Denmark). Prior to this animal experiment, we confirmed that the blood gas analyzer indicated compatible values when samples were diluted by saline including different concentrations of LEH. Hemodynamic parameters were recorded before CPB and at 5, 10, 15, 30, 60, 90, and 120 min after initiation of CPB. Blood samples were analyzed at the same times.

Arterial oxygen content (CaO2), venous oxygen content (CvO2), arteriovenous oxygen difference (AVDO2), oxygen delivery (DO2), cardiac output (CO), systemic vascular resistance (SVR), and VO2 were calculated from data obtained from the experiment:

$$CaO2 = 1.34 \times Hb \times SaO2 + 0.003 \times PaO2 \text{ (ml/dl)}$$
$$CvO2 = 1.34 \times Hb \times SvO2 + 0.003 \times PvO2 \text{ (ml/dl)}$$
$$AVDO2 = (CaO2 - CvO2) \text{ (ml/dl)}$$
$$DO2 = CaO2 \times \text{systemic flow*} \text{ (ml O2/kg/min)}$$
$$CO = VO2/AVDO2 \text{ (dl/kg/min)}$$
$$SVR = (mAP\text{-}CVP) \times 79.92/\text{systemic flow } (\text{dyne}\cdot\text{s/cm}^5)$$
$$VO2 = AVDO2 \times BF \text{ (ml O2/kg/min)}$$

where systemic flow* means cardiac output in the pre-CPB condition or bypass flow during CPB.

When the hematocrit and LEH volume concentration were measured, 1 ml of 8% dextran (D4876, Sigma-Aldrich, MO, USA) was added to the same amount of whole blood before the mixture was centrifuged for 10 min at 12 000 rpm. For serum chemistry, the whole blood sample was centrifuged for 10 min at 3000 rpm. The addition of 1 ml of 35% dextran into the same amount of the supernatant was followed by centrifugation for 30 min at 3000 rpm. The supernatant of this mixture was used for serum chemistry analysis. For histopathological examination, the animals were killed under anesthesia after 120 min of CPB. Samples from the brain, heart, lungs, liver, spleen, and kidneys were fixed for several days in 10% neutral buffered formalin. The specimens were stained with hematoxylin and eosin after embedding in paraffin wax and were examined with a light microscope.

Results

Hemodynamics

In the pre-CPB condition, the mean aortic pressure was 80 ± 18 and 82 ± 18 mmHg in the LEH group and control group, respectively. After initiation of CPB, mean aortic pressures remained between 47 and 61 mmHg in the LEH group and between 41 and 50 mmHg in the control group (Table 1).

Mean bypass flow was maintained between 103 and 118 ml/kg/min in the LEH group and between 109 and

Table 1. Hemodynamics of kid goats undergoing cardiopulmonary bypass

	CPB time	Control group	LEH group
mAP (mmHg)	Pre-CPB	80 ± 18	82 ± 18
	30 min	41 ± 3	53 ± 4
	120 min	47 ± 18	61 ± 14
CVP (mmHg)	Pre-CPB	14 ± 1	11 ± 6
	30 min	13 ± 6	10 ± 5
	120 min	12 ± 6	11 ± 6
Systemic flow (ml/kg/min)	Pre-CPB	157 ± 46	150 ± 77
	30 min	111 ± 17	103 ± 34
	120 min	115 ± 10	116 ± 4
SVR (dyne·s/cm^5)	Pre-CPB	1576 ± 627	2437 ± 1670
	30 min	995 ± 335	1851 ± 1154
	120 min	1135 ± 508	1617 ± 709

116 ml/kg/min in the control group. The calculated mean systemic vascular resistance had a tendency to be higher in the LEH group (1348–1918 dyne·s/cm^5) than in the control group (935–1205 dyne·s/cm^5).

Oxygen carrier concentration

Liposome-encapsulated hemoglobin volume concentration was maintained at 5% ± 1% for 120 min after initiation of CPB. The values of hematocrit decreased by half after initiation of CPB in both groups: 34% ± 6% to 15% ± 4% and 33% ± 6% to 16% ± 3% in the LEH group and in the control group, respectively. Similarly, hemoglobin concentrations also decreased by about half after the initiation of CPB in both groups: 10.5 ± 2.0 to 6.3 ± 1.5 g/dl and 10.5 ± 1.4 to 6.2 ± 1.3 g/dl in the LEH group and in the control group, respectively. There were no major differences in hematocrit and hemoglobin concentrations between the LEH group and the control group.

Oxygen metabolism

The calculated oxygen delivery similarly decreased after initiation of CPB in both groups: 21.0 ± 10.3 to 11.0 ± 2.0 ml/kg/min and 20.9 ± 4.8 to 11.0 ± 2.3 ml/kg/min in the LEH group and in the control group, respectively (Fig. 1). Meanwhile, venous oxygen saturation in the LEH group (82%–85%) had a lower trend than that in the control group (86%–89%) throughout the experiment. Thus, the calculated oxygen consumption in the LEH group (2.5–2.7 ml/kg/min) tended to be higher than that in the control group (2.4–2.5 ml/kg/min), as shown in Fig. 2.

The lactate concentrations reached their highest levels 30 min after initiation of CPB in both groups: 25.0 ± 2.9 and 23.8 ± 11.1 mg/dl in the LEH group and in the control group, respectively. Thereafter, the concentrations decreased similarly. In contrast, the pyruvate concentration stayed at the same level (1.0 ± 0.5 mg/dl) in the control group beyond 30 min after initiation of CPB, whereas the pyruvate level continued to increase in the LEH group. Therefore the ratio of lactate/pyruvate tended to decrease earlier in the LEH group than in the control group (Fig. 3).

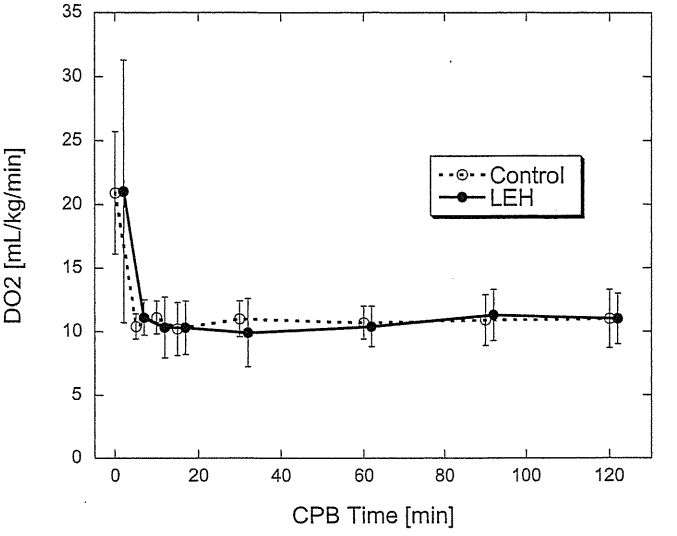

Fig. 1. Oxygen delivery rate (*DO2*) before and during cardiopulmonary bypass (*CPB*) in kid goats. *LEH*, liposome-encapsulated hemoglobin

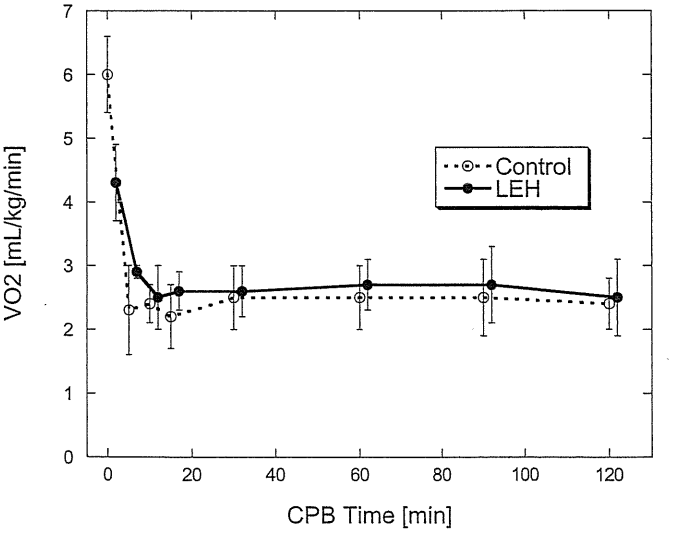

Fig. 2. Oxygen consumption rate (*VO2*) before and during CPB in kid goats

Histopathological examination

Histological examination showed no significant change in either group. No hemosiderin deposit was observed in the reticular system in the LEH group.

Discussion

CPB with hemodilution has been proposed as a useful method for many types of cardiovascular surgery. However,

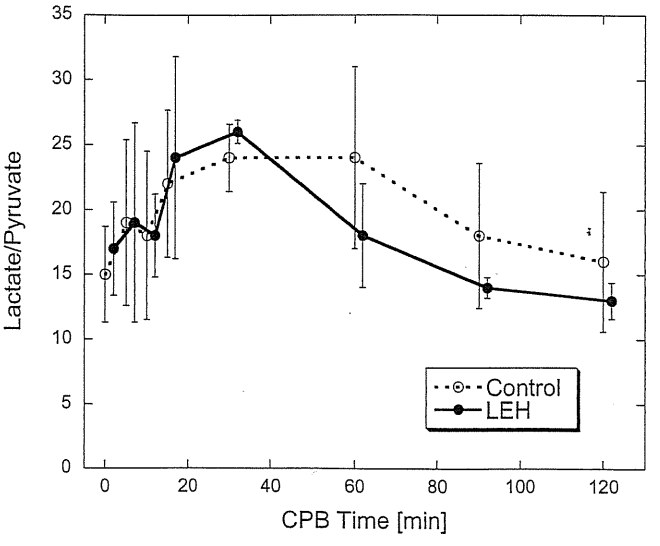

Fig. 3. Blood ratio of lactate to pyruvate before and during CPB in kid goats

hemodilution in CPB causes some adverse effects, including decreasing oncotic pressure and acute anemia followed by hypoxemia. Especially in small pediatric patients, CPB without transfusion results in massive hemodilution that has an impact on mortality and morbidity.

Although the harmful effects of severe hemodilution need to be prevented, blood transfusion should be avoided whenever possible because of the possibility of infection and pathological immune reaction, including graft-versus-host disease.

Therefore, we have been developing a new CPB technique using LEH. We expected that combined therapy using LEH would improve oxygen metabolism in the peripheral tissue during hemodiluted CPB without serious adverse effects. In this study, we measured oxygen consumption before and during CPB to evaluate the effect of LEH on alleviation of the decrease in oxygen metabolism during with hemodilution CPB.

Although the hemoglobin concentration during CPB in the LEH group was estimated to be 1 g/dl higher than that in the control group, the hemoglobin levels were almost the same in both groups. We supposed that the amount of LEH applied in the pump-priming solution in this study was not enough to increase the hemoglobin level.

Because the hemoglobin levels were almost the same in the two groups, the oxygen delivery was also the same, as shown in Fig. 1. Oxygen consumption in the control group, however, had a tendency to be lower than that in the LEH group (Fig. 2). This difference may have been caused by additional oxygen delivery from LEH to the peripheral tissue where oxygen consumption was suppressed due to deficiency of oxygen delivery. The fact that the values for oxygen consumption before CPB were higher than those during CPB in both groups implies restricted oxygen delivery during CPB.

Additionally, we measured the serum lactate and serum pyruvate levels to assess the oxygen metabolism. The serum pyruvate concentrations tended to be higher in the LEH group, whereas the serum lactate concentrations were almost the same in both groups. Insufficient oxygen delivery is associated with a sustained increase in the lactate/pyruvate ratio.[13] This increase is considered to be a manifestation of changes in cells' redox state consequent to an inadequate supply of oxygen to the mitochondria.[14] In this study, although lactate/pyruvate initially increased in both groups after initiation of CPB, it decreased earlier in the LEH group, suggesting that an aerobic environment was restored to the tissue earlier in the LEH group after the initiation of CPB. This result also supports our hypothesis that LEH improves the reduced aerobic oxygen metabolism during CPB.

A limitation of this study is that the effects on organ function after weaning off CPB is unknown. Further study will be necessary to establish the combined therapy of CPB and LEH.

Conclusions

Application of liposome-encapsulated hemoglobin in the pump-priming solution can be anticipated to improve decreased aerobic oxygen metabolism during cardiopulmonary bypass without any serious adverse effects.

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