A Biomedical Engineering Study on the Physiological Effects of Left Ventricular Assistance

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論　文　内　容　の　要　旨

Chapter 1 - Introduction

Heart failure incidence has increased in the past decades and this disease constitutes a major public health problem in most industrialized countries. The lack of a viable treatment available motivated the development of artificial hearts. The development of those artificial hearts have reached enough progress be permit the clinical usage of those devices. However, before the successful insertion of artificial hearts in the clinical field, there is a gap between medical field and engineering field that has to be filled.

Engineers have developed pumps that are robust enough to be used for years and were able to solve problems related to hemolisis and thrombogenic event. On the other side, medical doctors presented outstanding results in clinical trials of those pumps. However, hemodynamical changes caused by a VAD are not commonly considered in the development of pumps and technical differences among pumps are not taken in consideration by physicians. This study links those two fields aiming at permitting an optimal usage of pumps according to the physiological conditions of each patient and at providing necessary information for the development of next pumps and future control approaches.

With that objective, three main problems were solved in this study. The first one was the lack of a model to predict circulatory equilibrium during circulatory mechanical support. Next, we compared two centrifugal flow pumps clarifying the physiological effects of some particular design features that each of them have. Finally, for the ventricular assistance, the monitoring of the native cardiac function is important, the lack of a reliable cardiac function index that could be used also during assistance was the third problem approached.

Chapter 2 - Fundamentals on Native Cardiovascular System and Artificial Hearts

The cardiovascular system carries oxygen and nutrients to tissues in the body and carries away the

byproducts of metabolism. When the native heart function is impaired, the equilibrium and nutrition of all other organs and tissues is affected. Until recent years, the only treatment for chronic heart failure was the transplant, whose main limitation is shortage in donors. Nowadays, artificial hearts permit the patient to survive longer periods while waiting for an available organ for transplant (bridge-to-transplant). Those devices are also expected to be useful in long term supports (destination therapy) or unload the native heart in therapies that promote the myocardial recovery (bridge-to-recovery), representing a promising alternative for the treatment of heart failure patients.

There are two main kinds of artificial hearts. Total artificial hearts replace the native heart, while ventricular assist devices help the native ventricle to maintain the circulation. The pumps that are used are commonly classified accordingly to their flow patterns into pulsatile pumps and continuous flow pumps; the latter includes centrifugal and axial flow pumps.

Most of the recent applications are of continuous flow pumps as ventricular assist devices. In 2010, two continuous flow pumps have received permission of commercialization in Japan: Evaheart LVAS (Sun Medical Res. Tec. Co.) and Duraheart LVAD (Terumo Co.).

Chapter 3 - Prediction of Circulatory Equilibrium during Ventricular Assistance

Regulation of cardiac output (CO) and venous return (VR) to maintain the circulatory equilibrium is an important mechanism in the cardiovascular system. The characterization of the cardiovascular system equilibrium is important for the adequate patient care, *e.g.* in drug administration and setup of pump rotational speed. Circulatory equilibrium in intact circulation has been well explained by Guyton's framework. However, VAD imposes to the left ventricle loads that are out of the physiological range and also out of the range analyzed when the model was proposed. Therefore, there was no guarantee that the model would still be valid during mechanical cardiac support.

For an intact circulation the circulatory equilibrium can be expressed as the intersection of a VR surface and a CO curve, which represent blood flow against atrial pressure. VR surfaces are determined by volume of blood in the circulation, venous compliance and systemic vascular resistance. CO curves represent the cardiac performance.

In the case of a patient with ventricular assistance, we assumed that in the systemic circulation vessels see the native heart and the VAD as one pump, and that in the pulmonary circulation, VAD has no direct influence. Modeling the vascular system with distributed elements model, we obtained equations that related venous return to left and right arterial pressures.

Equations for CO curves were obtained from analysis of P-V loops based on end systolic ventricular elastance and arterial elastance. Stroke volume was defined as, different from in an intact circulation, the difference between maximal and minimal ventricular volume. The change in ventricular volume during isovolumic relaxation was calculated using a linear relation between this volume change and peak pump flow obtained from *in vivo* data.

The equations obtained for VR surface and CO curve were validated using data obtained in two animal experiments with young goats. Evaheart LVAS was connected in a bypass from the left ventricle to the

descending aorta. Pump rotational speed was constantly increased from 1200rpm to 2000rpm during 60s. Propranolol was administrated to induce a decrease in ventricular contractility for the validation of the model in two different inotropic states. 1l of ringer's solution with glucose (Lactec G) was injected in a rate of 150ml/min for validation of the model against changes of blood volume. Right atrial pressure and left atrial pressure were measured invasively with fluid-filled catheters. Pump flow and aortic flow were monitored with electromagnetic and ultrasound flow probes, respectively.

Results showed a good agreement between data obtained in animal experiments and the proposed model. The mean of the residue of the estimation of aortic flow using equations of VR surface was less than 0.4l/min; and when using equations of CO curve, it was less than 0.2l/min. Those results indicate that the pump and its assist rate did not influence the venous return surface model and that the pump can be included as one of the factors that influence cardiac performance.

Chapter 4 - Physiological Effects of Continuous Flow Pump Characteristics: a comparison between two pumps

In November 2010, two centrifugal continuous flow pumps received permission to be commercialized in Japan. Since then, they have already been implanted in many patients and the number of centers where they are available has also increased. Even though they are both centrifugal blood pumps, there are important structural differences between them that result in different head-flow (H-Q) characteristics. However, it was not known how those mechanical differences affect the cardiovascular system. In other words, there was no information on how to choose the most adequate pump for each patient. For the optimal usage of VADs, it is necessary to understand the physiological effects of the particular features of each pump.

In vitro and *in vivo* studies were performed to compare two centrifugal blood pumps. Since Evaheart and Duraheart have many particular features, in this study we compared Evaheart pump to Baylor Gyro pump, which has a conventional centrifugal pump structural design. First, those two pumps were compared in a mock circulation in order to obtain their H-Q characteristics in a same system. Next, both pumps were implanted in goats and the interactions between each pump and the native cardiovascular system were evaluated.

The mock system employed in this study was built with conventional pipe tubes. The mean used was room temperature tap water. Pump flow was measured at different levels of constant pump head. A considerable difference between H-Q curves of both pumps was observed. Evaheart pump showed a flat H-Q curve, while for Baylor pump characteristics were steeper, which suggests that flow of Evaheart pump is more sensitive to pump head.

Animal experimental data were measured in 6 adult goats. Two centrifugal pumps were connected in parallel in a bypass from left ventricle to aorta. Pumps alternately assisted the left ventricle in order to compare the physiological influence of each pump in similar physiological conditions. The outflow cannula was connected to the descending aorta and the inlet was inserted into the left ventricular apex. Blood flow through the aortic valve was measured by an ultrasonic flow probe on the ascending aorta. Pump flow was measured with an electromagnetic flowmeter. Additionally, blood pressure was also measured in the ascending aorta. Data were recorded at different rotational speeds, before and after

the injection of propranolol, which is a medicine that depresses cardiac function. Additionally, data were recorded when both pumps were off.

Changes on Evaheart pump flow were faster than the ones observed in Baylor pump flow. Depending on the native contractility, we observed backflow through Evaheart pump during filling and isovolumic contraction periods. No backflow was observed in Baylor pump. In general, pulsatility was promoted by the Evaheart pump assistance, which is beneficial for the perfusion of other organs and tissues and also important for the adequate regulation of the cardiovascular system.

However, when the native cardiac function was very low, Evaheart pump was not able to increase blood pressure or flow, even when rotational speed was high, in comparison to the unassisted heart. In such condition, Baylor pump seems to be more appropriated.

For an adequate peripheral perfusion it is important to maintain the cardiac output, which corresponds to the mean total flow, and also the systolic arterial pressure as well as its pulsatility. Although both evaluated pumps are centrifugal flow pumps, they have different H-Q curves due to their structures, which results in different physiological effects.

The progress from the development phase and the clinical application of ventricular assist devices requires further understanding of the physiological interaction between the circulatory system and the pump. The number of implanted patients will increase and it will not be possible for the physicians to follow up each of them so closely. Besides, understanding differences between each model will be useful for the appropriate choice of the pump for each patient, to interpret the response of the body to the pump settings and also for the implementation of an optimal pump control that maintains sufficient perfusion without causing suction of the ventricular wall at the same time as it promotes the myocardial unloading.

Chapter 5 - Detection of Myocardial Recovery during Ventricular Assist Device Support

In some patients, it was observed that the unloading promoted by VADs might permit the myocardial recovery, especially when combined with other treatments such as cell therapy. When the recovery of the native heart is detected, the pump can be removed, which results in a considerable improvement on the patient's quality of life. However, the pump unloading affects both blood flow and pressure; thus, the ventricular assistance might lead to a mistaken cardiac function assessment. Due to the invasiveness of pump's removal and an eventual re-implantation and to the risk of insufficient perfusion of other organs, it is fundamental that the recovery is correctly detected for a successful bridge-to-recovery.

Previously used pumps were pulsatile flow pumps which have mechanical valves in their inlet and outlet. During ventricular assistance with those pumps, it is possible to assess the cardiac function of the unassisted heart by stopping the pump. However, continuous flow pumps have no valves, therefore, stopping the pump is not effective to assess the cardiac function correctly and is also dangerous due to regurgitation.

During clinical trials, maximum ventricular elastance (E_{max}) and ejection fraction (EF) have been used

for the assessment of myocardial recovery in patients. However there are evidences that those and other conventional indices used for the assessment of cardiac function in an intact circulation are influenced by the ventricular assistance.

In this study, five conventional cardiac function indices were evaluated with *in vivo* data: E_{max}, *EF*, preload recruitable stroke work slope (M_W), maximal power-based index (M_{PWR}) and the maximum of the time derivative of ventricular pressure-based index (M_{dP}). Calculation method of each index was reviewed based on the hemodynamical changes induced by the VAD and were adjusted when necessary. *EF* was chosen due to its common clinical application. Other indices were chosen due to their low sensitivity to ventricular loading condition in an intact circulation.

Data were recorded in a similar setup to the described in previous chapters. In the experiments Evaheart pump (n = 7) or Baylor pump (n = 8), was connected in bypass from left ventricle to descending aorta. In six experiments, both pumps were implanted simultaneously. Additionally, left ventricular pressure and volume were measured with a conductance catheter inserted into left ventricle from the left atrium.

Results indicate that *EF* is affected by the pump because it could not detected changes in ventricular contractility imposed by Inderal injection. The correlation between M_{PWR} calculated for data during assistance and for the unassisted heart was low, indicating that the cardiac function assessed with this index during assistance do not represent the cardiac function that would be observed after pump removal. The other three indices could correctly detect cardiac function of the unassisted heart independently of pump rotational speed when assist rate was kept bellow 0.8.

The loading conditions that are imposed by VADs are outside the physiological range. It is important to re-validate cardiac function indices and other physiological parameters in this new environment. *In vivo* results indicate that the pump affects the analyzed indices. The results presented in this thesis are also useful in the development of new less invasive indices since they permit a reliable validation of such indices which was not possible before.

Chapter 6 - Conclusions

In this thesis the physiological effects of left ventricular support were discussed. Understanding those interactions is important for the correct patient's management, adjustment of pump rotational speed, choosing of the adequate pump according to the patient's condition, design of future pumps and their control algorithms and accurate detection of the native cardiac function.

Those findings are fundamental for the inclusion of VADs in the roll of treatments for heart failure. That knowledge together with recently developed pumps will permit the application of centrifugal pumps not only as a device that permits the patients to survive but also as a device that promotes the patient's quality of life.

論文審査結果の要旨

現在、患者の体内に埋込み可能な定常流補助人工心臓の臨床応用が進みつつある。しかし、定常流ポンプの装着が生体循環系に与える生理的影響はまだ詳しくわかっていない。また、人工心臓の離脱時期決定に重要な心機能の定量的評価法が未確立である。本論文は、埋込み型定常流人工心臓が循環系に与える生理的効果と循環制御に関する研究をまとめたものであり、全編6章から成る。

第1章は序論であり、本研究の背景および目的を述べている。

第2章では、生体循環系および人工心臓用ポンプの基礎について述べるとともに、本論文の研究対象である定常流補助人工心臓（EvaHeart pump およびBaylor Pump）の動作原理・特徴・基本特性および制御系の構造と機能について説明している。

第3章では、Guytonのモデルを基礎とし、補助人工心臓の装着が循環平衡に与える影響について成ヤギのデータにより検討した。その結果、循環平衡状態の変化が、Sugimachi らの方法を修正することにより説明可能であることを示した。これは、補助人工心臓が装着された循環系に対しても循環平衡状態を予測できることを意味するものであり、臨床応用上有用な成果である。

第4章では、上記2種類のポンプ特性の違いが循環系に与える生理的影響について、模擬循環系および成ヤギのデータに基づいて解析した。その結果、ポンプ特性の相違と心機能の強弱の組み合わせが脈圧・血流パターンに与える影響を明らかにすることができ、心機能の強さによって血液ポンプを適切に選択することの重要性が示唆された。これは、補助人工心臓を選択するための定量的根拠を与えるものであり、重要な知見である。

第5章では、補助循環下の成ヤギのデータに基づき、5種類の心機能推定指標の精度を求めた。その結果、負荷依存性の少ない指標の精度が高いこと、および補助率0.8以内での推定が重要であることを明らかにした。これは、補助人工心臓の離脱時期決定にとって極めて有用な知見である。

第6章は結論である。

以上要するに本論文は、定常流補助人工心臓制御システムの実用化に重要である循環平衡状態予測、ポンプ特性の相違が循環系に与える影響、および心機能推定指標の精度評価を動物実験により明らかにしたものであり、医用生体工学の発展に寄与するところが少なくない。

よって、本論文は博士(医工学)の学位論文として合格と認める。