implantable artificial organ in our Institute. This artificial esophagus enables the swallowing of food by peristalsis. It is a new and unprecedented invention that serves as a complete organ.

A simple tube called the "artificial esophagus" had been invented in the past. Of course, this tube did not perform peristalsis. A patient using it was unable to swallow food. In those days, a patient was externally implanted with an artificial esophagus. This old artificial esophagus did not produce peristalsis. The patient had to manually squeeze the external tube. Thus, such a system was not very useful.

We invented the world's first "artificial esophagus that performs peristalsis." We have already applied for a patent.

This system consists of the principal part of an artificial esophagus, an actuator, and a control unit. An artificial esophagus tube is made from high macromolecule, which has affinity to the body. It is planned to be equipped with a nano pressure sensor on the inner surface. The arrival of food is sensed and peristalsis automatically begins.

An actuator constitutes several shape memory alloy rings. The nano technology was used for the shape memory alloy (SMA) ring, and crystal structure was arranged. We have succeeded in developing a 50 micron shape memory alloy fiber. The SMA ring was further formed in the shape of a ring. The contraction distance was thereby significantly extended. When a ring contracted in order, peristalsis took shape.

We are now developing this system on the basis of the image data of the peristalsis of an esophagus fluoroscopy of the authors of this paper. Energy is transmitted by the transcutaneous energy transmission system. A complete implantation became possible by the application of this system.

Peristalsis was confirmed by the animal experiment. The esophagus was excised and the developed artificial esophagus was implanted. Peristalsis movement was observed as the satisfactory results..

Drinking stent project

An operation of an esophagus cancer is difficult. The esophagus cancer which advanced is not removable. The patient of the esophagus cancer, which is not excisable, cannot have a meal because of stenosis of the esophagus. A STENT is inserted in order to swallow a meal. However, a meal may be got blocked in a stent. In this case, an endoscope is required. A patient's pain is large when an endoscope is used.

Then, we invented the **Drinking Stent** which can swallow foods. A stent consists of a macromolecule material and a system of artificial peristalsis muscles. Artificial peristalsis muscles consist of Biometal(s).

In clinical cases, the nealy developed drinking stent is scheduled to be inserted, after extending a constriction using a balloon. Furthermore, we can apply this new stent for various kinds of stenting. For example, stent for the esophagus, intestine, bile duct, urinary tract will be embodied in future.

There will be a large market when we consider the various kinds of stent, thus, industrialization is under plan.

Therapeutic drinking stent

Cancer tissue invaded into the metallic stent, so, internal diameter cannot be maintained in these cases with progressing esophageal cancer. We are now developing therapeutic stent with healing effect with hyperthermia at the malignant tissue.

In our *therapeutic drinking STENT system*, 30-60min daily hyperthermia is noted as the treatment for the malignant carcinoma at the outsides of STENT. If we added this function by the electromagnetic induction to the drinking stent, the average survival time of the patients should be prolonged by the therapeutic effect of hyperthermia.

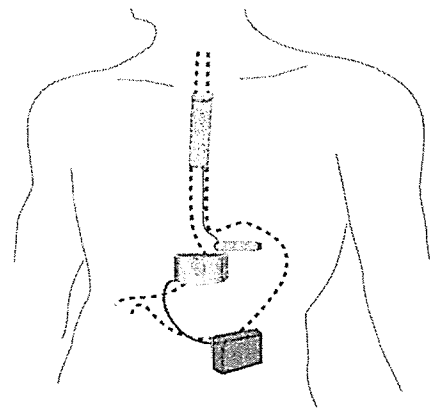

Fig.1 Theraeutic drinking stent

Furthermore, we can implant this system with only fiberscope without any invasion to the skin.

We are now developing the drinking stent with therapeutic effect.

Conclusions

Various kinds of artificial internal organs will be embodied in future by the use of the nano technology.

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特集 先駆的医工学と循環器

機械的補助循環*

山家智之**

Key Words：total artificial heart, ventricular assist device, rotary blood pump, axial flow pump

緒　言

救急車で心臓マッサージをしながら担ぎ込まれる患者様が，救命救急処置によって速やかに回復し，元気で退院してくれれば，救急病院の勤務医として医師冥利につきると考えられるが，現実にはもちろん，なかなかそううまくはいかない症例も数多い[1)~4)]．

とくに，心臓疾患で，心臓がプライマリーに傷害された心筋梗塞などの患者では，心拍は再開しても十二分な心拍出が得られず，回復するまでの間，心機能の補助が必要になる症例は数多い．薬剤抵抗性の重症心不全では，循環を維持するために機械的補助循環が必要になる症例は増加しつつある．また，心臓手術のあとにもっとも注意を払わなくてはいけないポイントの一つに心ポンプ作用があげられる．術直後から数日にわたる心ポンプ作用(心収縮力)の低下に起因する心不全をとくにlow output syndrome(LOS)と呼ぶことが多い．ここでは，LOS，心不全時における機械的補助循環について述べる[5)6)]．

大動脈内バルーンポンピング(IABP)

緊急時に救命救急の現場でもっとも簡便にアプリケーションが簡単なデバイスとしてIABPがある[7)8)]．大腿動脈が触れるだけの脈圧があれば，緊急でさっと消毒して，まっすぐに大腿動脈を穿刺し，シースカテーテルを挿入し，シースを介して下行大動脈までバルーンカテーテルを進める．原則として透視下で挿入され，位置を確認するのが原則であるが，救急の現場ではブラインドでも挿入可能である．

心臓の拡張期に合わせて下行大動脈にてバルーンを膨らませることにより，強力な血圧の補助効果があり，拡張期の血圧上昇により冠動脈血流を増加させ，収縮期は心臓の負荷を軽減させる作用があるので，とくに虚血性心疾患には有効である．

開発された当初はカテーテルの径も大きく，抜去後の出血もあり，大腿動脈に人工血管を縫合して導入するのが原則となっていたが，高分子化学の進展とともに，薄くても耐久性に優れた素材や設計方式が開発されるにつれ，現在は，昔の冠動脈造影カテーテルや，PTCAカテーテルと差がない8フレンチのバルーンカテーテルも開発されるようになり，内科医が気軽に応用するようになって症例数が爆発的に増加した．

現在は，PTCA後に，若干血圧が低めの例に，冠動脈の血流改善を期待して挿入される例もあり，補助循環としてだけではなく，心筋虚血の治療としても応用されるようになってきている．

しかしながら，IABPは，血液を循環させるポンプシステムではなく，シンプルにバルーンを

* Mechanical circulatory assistance.

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膨らませているだけなので，血圧の補助には大変に有効であるが，本格的な心不全におけるポンプ失調にはあまり有効でないとの報告も散見される．一説には，IABPは，圧補助としては強力であるが，流量補助効果としては心拍出量の10%前後にすぎないという説もあり，流量補助が必要な重症心不全では，さらに強力な補助手段が求められる．たとえば次に述べるPCPSなどである．

Percutaneous cardiopulmonary support system (PCPS)

心肺停止状態でもっとも信頼できる治療法の一つとして，人工心肺システムがある．心臓手術に使われる人工心肺システムは，心臓と肺の機能を完全に代行できるので，原理的には完全な心肺機能停止状態にも対応できる強力な救命手段ということになる．しかしながら，心臓手術中に，胸を切り開いたあとに，ゆっくりと取り付けるのが本来の人工心肺のあり方であるから，緊急時にはなかなか救急現場でアプリケーションを行うことは難しかった．そこで開発されたのがPercutaneous cardiopulmonary support system (PCPS)であり，経皮的に，大腿動静脈を穿刺することで比較的簡便に装着することが可能である[9)~11)]．このシステムの臨床応用により，救命率は飛躍的に向上してきた歴史がある．

しかしながら，PCPSシステムは人工肺の部分も含有するので，ヘパリン付加を行っても，自ずとサポート時間に限界がある．また，人工心の部分を構成するロータリーポンプは体外循環用のものなので，24時間を超える使用は原則として推奨されない．

残念ながら24時間以内にすべての心臓病が回復するわけではないので，循環補助が長期に必要とされる病態では，補助人工心臓，全置換型人工心臓，そして心臓移植など，さらに強力な救命手段が必要になる．

人工心臓

2005年7月，東京女子医科大学において初の国産ロータリーポンプ(RP)型人工心臓の臨床応用が報告され話題を呼んだ．単なる遠心力を応用した回転式ポンプであるRPで代用できることからもわかるように，心臓は主に血液循環を司るポンプの役割を果たしており，全身から心臓に戻ってきた血液は肺循環に送り出されたあと，再び心臓に戻り，最後に全身へと送り出される．

表1 人工心臓

1. 全置換型人工心臓
2. 補助人工心臓
   2-1. 左心補助人工心臓
      2-1-1. 左心房脱血・大動脈送血
      2-2-2. 左心室脱血・大動脈送血
   2-2. 右心補助人工心臓

したがって，「人工」心臓とは，このポンプ機能を，機械的に補助，代行させるシステムと定義されるということになる．したがって，IABP，PCPSも，ポンピング機能に近い機能は保持していることになるが，一般に人工心臓として扱われるのは，補助人工心臓，全置換型人工心臓などである[12)~18)]．

欧米と比較して，心疾患が少ないといわれてきた日本では，人工心臓にはそれほどの需要はないとも考えられてきたが，近年の食生活の欧米化などによる心血管イベントの増大や，高齢化社会の到来を向かえ，日本でも人工心臓を含めた補助循環が必要になるような臨床現場における局面はますます拡大しつつあるのが現状であるといえる．

世界的にみれば，人工心臓は大きく分けて2種類が臨床応用されている．1つは自分の心臓(心室部分)を取り除いて，2つの血液ポンプに完全に置換してしまうもので，全置換型人工心臓と呼称される．もう1つは自分の心臓は残して，心房や心室と呼ばれる場所から血液を脱血して，ポンプで大動脈へ返血する補助人工心臓と呼ばれるものである．さらに補助人工心臓は，左心の体循環を補助する左心補助人工心臓，右心系の肺循環を補助する右心補助人工心臓に大別される．心筋梗塞などにおける重症の左心系のポンプ失調には左心補助人工心臓が用いられ，肺高血圧症などで右心の肺循環が維持できない患者には右心補助人工心臓が用いられる(表1)．また，左心補助人工心臓では，左心房からバイパスして大動脈へポンプ送血するタイプと，左

心室から脱血するタイプの2種類がある．心臓手術後の一時的LOSでは，左心房から脱血して心機能を温存して，回復ののち，補助人工心臓からの離脱を図る病態もあり，心臓移植までのブリッジでは，左心室脱血で，十分なポンプ流量を維持することが必要な病態もある．

1．全置換型人工心臓

まず全置換型人工心臓の歴史を紐解けば，1959年に阿久津らにより最初の人工心臓の動物実験が報告されて以来，人工心臓開発の目的は永久使用であった．しかしながら，出血・感染・多臓器不全・材料の耐久性など，さまざまな問題のためになかなか長期使用に耐えうるものが完成しなかった歴史がある．早くも60年代には，全置換型人工心臓の最初の臨床応用の報告があるが，移植心を待つ間の生命維持のための緊急避難的な要素が大きい症例であった．その後，動物実験の成績の向上を受けて，80年代初頭から本格的に臨床応用が開始された空気圧駆動型の全置換型人工心臓ジャービック7は，メディアなどにも大きく取り上げられ，「人工心臓」の存在を世に広めた功績がある．しかしながら，ジャービック7の臨床試験では，最長で620日の生存は得られたものの，全例に脳血栓症をきたし，到底QOLに優れた臨床試験成績とは言い難く，この技術の難しさもまたあらためて広まってきた．

2001年ケンタッキー州のルイビル大学で，完全埋め込み型の全置換型人工心臓アビオコアの臨床応用が開始された．経皮エネルギー伝送システムの応用により，完全埋め込み型への進歩がみられ，空気圧駆動型のシステムのように，患者はエアチューブで駆動システムに固定されることはなく，感染の危険も少なくなった．しかしながら，現在のシステムはまだ大柄なアメリカ人男性には埋め込めても，小柄な日本人には到底埋め込むことはできない．そこで全置換型人工心臓に関しては，小柄な東洋人のための独自のシステム開発が進められている．

国立循環器病センターでは，NEDOなどのプロジェクトを介して小型埋め込み型全置換型人工心臓のシステム開発が進められており，エレクトロハイドローリック方式で，シリコンオイルを介して油圧式に左右の人工心臓を拍動させるメカニズムで，現在までに3か月近い動物実験における長期生存に成功している．

東京大学では，東北大学・北海道大学・北海道東海大学・早稲田大学・九州大学などと共同で，医薬品機構のサポートを受けて波動型全人工心臓開発プロジェクトを進めている．

末期的な重症心不全のもう一つの治療法である心臓移植は，技術的にも長足の進歩を遂げ，治療法の一つとして確立されていき，本邦でも脳死移植法案の成立により日常診療の中に位置を占めるに至っているが，ドナー不足が全世界的にみても深刻な問題となり，移植症例は頭打ちとなりつつある．そんななかで登場してきたのが移植までのつなぎ(ブリッジ使用)としての人工心臓の応用である．ジャービック7の時代には，人工心臓本体が体内に植え込まれ，体外の大きな駆動装置とはケーブルで連結されていたが，この大きな機械は少しずつ小型になり，アビオコアではついに完全埋め込み型に至っている．しかしながら，大型で東洋人に埋め込みが不可能なシステムであるので，国立循環器センター型人工心臓や波動ポンプの実用化が待たれる．

2．補助人工心臓

一説には補助循環を必要とする症例の約9割は，補助人工心臓のみで循環の維持が可能であるとされる．補助人工心臓は，開発当初は主として心臓手術後のLOSに対するデバイスとして一時使用を目的に開発されたが，手術後の補助人工心臓適応患者でも，約半数は補助人工心臓から離脱できず，半永久的な使用が必須となる．そのために，長期的に臨床で用いられる補助人工心臓の目的は，大きくは2つに分けることができる．1つは半永久的に人工心臓に依存して血液循環を維持するもの(永久使用)であり，もう1つは心臓移植のドナー(心臓の提供者)がみつかるまでの一時的な使用を目的とするもの(ブリッジ使用)である．ブリッジ使用の場合でも，現在の日本では，心臓移植までの待機時間は平均2年半にも及び，半永久的な使用を余儀なくされているのが現状である．

長期的な待機時間のブリッジ使用においても，

表2 補助人工心臓

1. 空気圧駆動型体外設置補助人工心臓
2. 埋め込み型補助人工心臓
   2-1. 拍動型補助人工心臓
      ノバコア
      ハートメイト
      ライオンハート
   2-2. 無拍動型補助人工心臓
      2-2-1. 遠心ポンプ
      2-2-2. 軸流ポンプ

半永久的な補助人工心臓の応用においても，超長期の埋め込みが前提になる以上，現在本邦で汎用される体外設置型の空気圧駆動型補助人工心臓だけでなく，完全埋め込み型の，感染の危険がなく，自宅へ帰れるシステムの開発へ向かうのは時代の趨勢である．

完全埋め込み型の補助人工心臓システムとしては，アメリカで開発されたノバコア(World Heart)とハートメイト(Thoratec)が先行しており(表2)，日本でも臨床試験に供されたが，ともに日本人の平均の体格の成人に埋め込むにはやや大きく，70kg以下の体格の症例には推奨されない[19]．

そこで，より小柄な体格の症例のために，遠心ポンプや軸流ポンプなどの無拍動ロータリーポンプが臨床に供されて注目されている．最初に臨床応用されたのは，小型のスクリューをもつ軸流ポンプのマイクロメドポンプ(Micromed)で，その後，ジャービック2000(Jarvik Heart)，ハートメイト2(Thoratec)，インコア(Berlin Heart)などの軸流ポンプが次々に臨床に供され，世界中で競争されている．現在，ジャービック2000の最長の生存例は5年を超え，2005年の米国人工内臓学会では，最長生存の患者自らが，自分の症例の症例報告を，自ら行って注目を浴びた[20]．

遠心ポンプはスクリュータイプの軸流ポンプと比較して，回転数が少なくてすむので，耐久性や溶血の観点で有利であり，世界中で開発が進められつつある．最初の臨床応用は，オーストラリアからベントラコア(Micromedical)の報告が行われ，クリーブランドからコアエイド(Arrow)，日本のテルモもヨーロッパでデュラハート(Terumo)の臨床試験を開始した．2005年に入り，ついに日本でもエバハート(Sun Medical)臨床試験が開始され，マスコミをにぎわせたのは記憶に新しい．

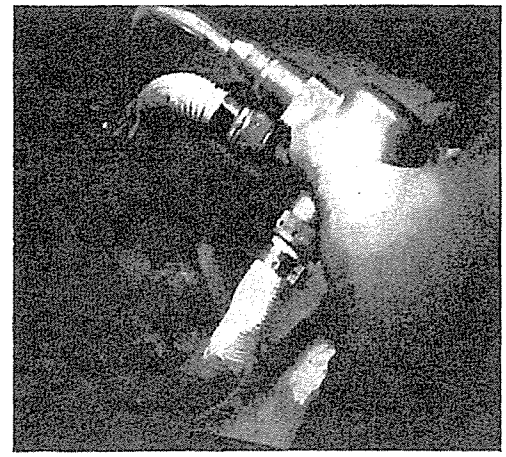

図1 動物実験中のエバハート

図1に，動物実験におけるエバハートの写真を提示する．体重50kgの山羊の胸腔内に容易に埋め込み可能であった．とくに送脱血カニューラがキンキングしないよう工夫が凝らされており，外科医の開発者ならではの手術の容易さが印象的なシステムである．東北大学では1年の長期生存実験を目指して，現在4か月目の山羊がオンゴーイングで生存中である[18]．

人工心臓は重症末期心不全の治療方法として着実に進歩しており，歴史を顧みると，米国でも日本でも，創成期から現在に至るまで多くの日本人研究者がかかわっており，日本の功績が大きい分野である．今後日本でのますますの発展が期待される．

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Implantable Brain Monitoring and Control Device by the use of Nano technology

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Abstract:

Seizure attack is an important symptom when we consider the quality of life of the patients with epilepsy. In some institute, implantable electrodes for recording EEG were used for the diagnosis of the focus. However, it was not implantable device and there is risk of infection and long term recording was impossible. Furthermore we need information of an another anatomical and pathological findings like blood flow, et al. by the use of CT, MRI, SPECT. In this study, new implantable monotoring system of the brain function was developed by the use of nano technolofgy, Nano DLC sensrs was used for the multichannel monitoring of brain focal blood flow and EEG signals. Energy was trasferred by the use of transcutaneous energy transmission system with nano particle. Focus of the epilepsy was controlled by the Peltier elements. Control unit was constituted by the nano microtip computer. By the use of this implantable system, brain function may be controlled with implantable device in future

Introduction

0.5-1.5% of general population have the Epilepsy. 20% of the patients cannot be controlled by the medication. For the control of the seizure attack, surgical resection of the epilepsy focus must be considered. However, complication must be considered in the surgical resection.

If we can control the seizure attack without surgical resection, it will be helpful for the patients with epilepsy

In this paper, new artificial organ for the monitoring and control of the brain function was proposed and basic design concept was reported and discussed

Nano sensors for brain function monitoring

We had invented new nano sensor consisted from Diamond like carbon Nano composite. Thickness of this DLC nano sensor is about 20 micron and by the changing of the dopping metal we can check various patho-physiological informations including pressure, temparature, and various chemical parameters.

Bio compatibility is so efficient and it is very thin film, so we can easily apply this sensor as the implantable sensors for artificial internal organs. In this study, we use this DLC nano sensor to record the brain function.

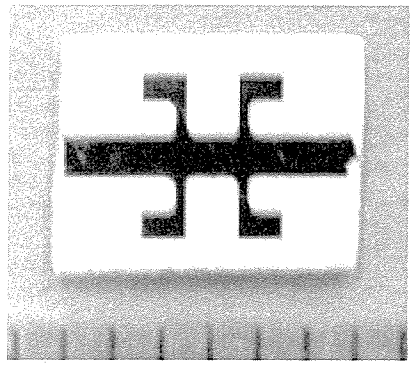

Fig.1 DLC nano sensing device

Anatomical fitting of the brain functional monitoring

For the diagnosis of the epilepsy focus for the surgical resection, implantable electrodes for multi channel EEG recording was used in the hospital. However, electric wire penetrate the skin, so, there is a risk of infection. Thus, long time recording is difficult in this system. If the seizure attack is not happened during recording, the diagnosis of the focus of epilepsy is failed (1-4).

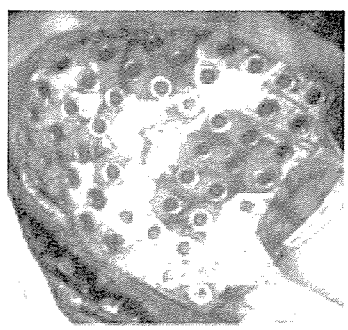

Fig.2 Imtracranial EEG multichannel electrodes for the diagnosis of the focus of epilepsy attack

In our plan, multi channel DLC nano sensor was implanted and information from brain was recorded from the transcutaneous energy transmission system (TETS) and transcutaneous information transmission system (TITS). By the adopting of these systems, long time recording without infection risk was embodied.

Control of brain function

In the several previous reports, seizure attack can be controlled by the focal cooling. We had invented the focal cooling machine by adopting the Peltier element. By adopting this system, we can control seizure attack by the implantable device.

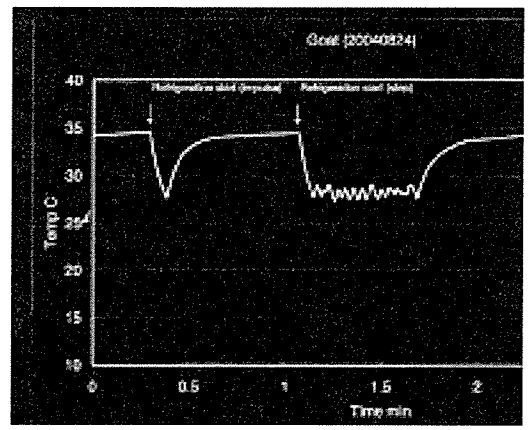

Fig.3 An example of the time series data of brain temperature during the cooling by the use of Peltier element

When the epilepsy attack was prevented by the implantable DLC nano sensing units, the diagnose program check the seizure and Focal cooling machine control the attack automatically in our concept.

Fig.3 showed the time series data of temperature of the brain tissue during the animal experiments. The Peltier elements worked well and cooling of the tissue was embodied.

In conclusion, we can embody the new implantable artificial organ, which can monitor and control the brain function by the use of Nano technology. This concept may be useful when we consider the higher dimensional brain functional monitoring and control.

Acknowledgements:

This work was partly supported by a Grant-in-aid for Scientific Research (11480253), the Program for Promotion of Fundamental Studies in Health Science for Organizing Drug ADR Relief, R&D Promotion and Product Review of Japan, Research on Advanced Medical Technology in Health, and Labor Sciences Research Grants (H14-Nano-020), Research Grant from Fukuda Memorial medical Technology Promotion Foundation, and Research Grant from Center for Interdisciplinary Research, Tohoku University.

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ARTIFICIAL ORGAN RESEARCHIN 21ST COE PROGRAM OF TOHOKU UNIVERSITY

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Abstract: Tohoku University was chosen as the first COE research institution in the 21st century. Various artificial organs, such as an artificial heart, an artificial myocardium, an artificial esophagus, and an artificial sphincter muscle, are now under development. There are common technologies for various internal artificial organs. The Nano sensing device, transcutaneous energy transimission system (TETS) and surface materials are common in various kinds of the artificial internal organs. So, it may be convenient to develop various kinds of artificial organs in one University。

Introduction

As for an implantable type artificial organ, a space for implantation is restricted. Therefore, micro device development is indispensable (1-11). Nanotechnology and micromachining technology development are very important. In Tohoku University, various artificial organ development is furthered according to the tradition of Nano machine micro machine development. In this paper, progress in various artificial internal organ projects were described

Artificial myocardium with Nano Technology .

The purpose of this research is developing nano artificial myocardium. Therefore, nano actuator, nano sensor, nano-microtip PC, nano fluid dynamics, nano TETS were studied in this project.

Especially, control-objectives value setup which imitated baroreflex system is tried using a nano sensor and a nano micro control chip. As a nano sensor, by this research, the nano thin film sensor adapting diamond-like carbon (DLC) was developed, and it applied for the patent (application for patent 2003-317956). The outstanding biocompatibility can be expected and the application to the artificial organ of all fields can be expected. Furthermore, the nano sensor adapting an optical fiber was also developed and it succeeded in the animal experiments. Since

information, such as each ventricle, can be evaluated simultaneously, the optimal drive of artificial myocardium is possible.

A hemodynamics is checked by the nano sensor and it is expected that a patient's life prognosis is sharply improvable by controlling an artificial myocardium optimally. The actuator in which nano micro-machining is also possible is used for the artificial myocardium which this research develops.

An artificial myocardium is a system with which the pulsation of the heart is assisted. The external surface of the heart is equipped with an artificial myocardium. Therefore, like the conventional artificial heart, there is no risk of a thrombus and it does not have the problem of the durability of an artificial valve. When there is no necessity, an artificial myocardium does not operate, and since circulation is performed only with the heart, improvement in the durability of an artificial-myocardium system is expected.

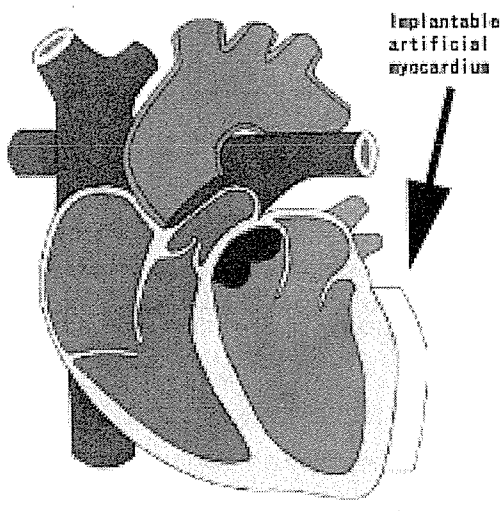

Fig.1 Schematic illustration of the implantable artificial myocardium

Development of an artificial esophagus which can drink by the use of Nanotechnology .

An about 10,000 Japanese per year died with an esophagus cancer. Everybody know that an operation of an esophagus cancer is difficult, because the reconstruction of an esophagus is needed. An operation will become easy if there is an artificial esophagus. An esophagus moves food by peristalsis. An simple pipe is not enough as an esophagus.

We invented the esophagus in which a peristalsis is possible. The developed artificial esophagus consists of a macromolecule material and artificial peristalsis muscles. Human's esophagus can swallow a thing by peristalsis. In order to realize a peristalsis, the shape memory alloy ring was used. The coil was made from the fiber of the shape memory alloy which improved durability by nanotechnology molecular crystal arrangement (Biometal, Toki Co., Tokyo, Japan).

The ring of a coil contracted in order and the peristalsis took shape. The animal experiment using the goat of the same weight as Japanese people was tried. The developed artificial esophagus was replaced with the excised esophagus. It was confirmed that the peristalsis had been realized in the body of a goat.

By the artificial esophagus, an operation of an esophagus cancer becomes easy. In the future, we can undergo an operation using an endoscope with artificial esophagus. Since there is little invasion, an operation of an old man will become possible. It is expected that invention of the artificial esophagus with peristalsis brings big progress to esophagus cancer surgical therapy.

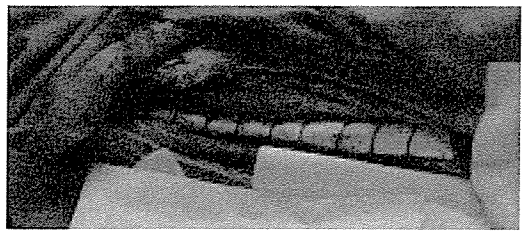

Fig.2 A photograph of an Artificial Esophagus, which can drink, after implantation

Project: Artificial Sphincter

Tohoku University invented the completely new artificial organ named artificial sphincter muscle as a completely implantable artificial organ.

Several patients must have Stoma following an operation of cancer of the Colon. An ostomy patient cannot control defecation . The artificial sphincter that we invented makes it possible for a patient to control defecation.

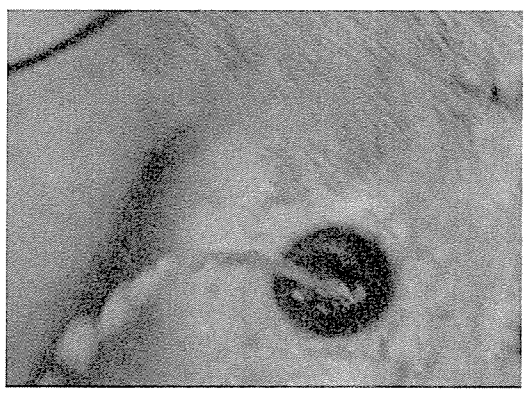

Fig.3 A Photrgaph of an animal experiment of the Artificial Sphincter during opening.

Therefore, we used the shape memory alloy. Two boards of a shape memory alloy were combined. A cushion was placed on the internal surface of a board to prevent tissue injury. Energy was transmitted by the transcutaneous energy transmission system (TETS). When a patient goes to a toilet, a patient brings TETS. TETS will be used, if a patient goes to a toilet and prepares(20-22) An artificial sphincter muscle opens and enables a patient to defecate. A patient can control defecation if this system is used. Thus, a patient's quality of life (QOL) will be improved greatly.

We wish to supply to a medical market soon.

Conclusion

Based upon various basic technologies, a lot of kinds of artificial internal organs can be carried out in Tohoku University. Further expansion of research theme can be expected in near future.

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Effect of ACE inhibitor on Baroreflex system evaluated with mathematical model, an artificial heart model and human being

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Abstract:

Several investigators suggested that ACE inhibitor and ARB are the important antihypertensive drugs when we consider the sensitivity of the baroreflex system. In this study, effect of sensitivity of the baroreflex system was evaluated with non-linear mathematical model, animal experiments using artificial heart with artificial baroreflex system, and HRV of the patients with essential hypertension before and after the drug administration. As the results, nonlinearity of the mathematical model induced chaotic dynamics, and these results was confirmed with artificial baroreflex system with artificial heart. Furthermore, after the drug administration, fractal dimension of the chaotic dynamics of the HRV altered significantly, suggesting the feasibility of the mathematical model and artificial heart model. These results in this study suggested the importance of the baroreflex sensitivity in chaotic behavior in hemodynamics.

Introduction

Everybody knows that hypertension is one of the most important risk factor, when we consider the cardiovascular events including ischemic heart disease, stroke, etc...and so on. Several investigators had suggested that baroreflex system play an important role in the pathophysiology of the essential hypertension.

As we easily found in the textbook of physiology, the Homeostasis maintain the hemodynamic derivatives within normal range. When the blood pressure increases, the baroreceptor can detect this increase. This information is evaluated by the central nervous system. And Heart Rate (HR) decreased by the autonomic nervous system. Cardiac output is decreased by the decrease of HR. And finally, blood pressure will be decreased and returned to normal range. This control system is called the Baroreflex system.

If the sensitivity of the baroreflex system is reduced, increase of the blood pressure cannot be compensated. So, blood pressure cannot be returned to normal value even during the increase of the blood pressure. By this reason, blood pressure is maintained in the high order and hypertension will be maintained.

Recenrly, various anti hypertensive drugs were used in the clinic. Especially, usefulness of ACE inhibitor and ARB showed important topics when we consider the sensitivity of the baroreflex system.(1-3)

In this study, this baroreflex system is simulated with electrical circuit model by the

computer system using non linear mathematics, and animal model using an artificial heart with artificial baroreflex system. And this thesis was utilized in the clinical actual data by the use of non-linear mathematics.

Computer simulation of the baroreflex system using electrical circuit model with non linearity.

In 1996, Cavalcanti et al. reported the electrical circuit model of the systemic circulation and baroreflex system with nonlinearity in IEEE(4), and found the occurren ℃ e of fluctuations like human being in the time series data of simulation.

Based upon this interesting challenge, real data of human being was introduced to the electrically simulated systemic circulation with baroreflex system. And the Nonlinear mathematical analysis was performed.

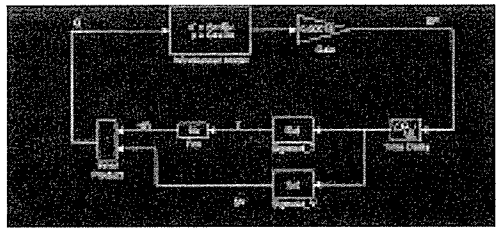

Fig.1 Electrical circuit model of the systemic circulation with baroreflex system including non linearity

By the use of this electrical circuit model, an interesting phenomenon was observed in the simulated time series data. If we altered the time lag of the baroreflex system, non linear behavior of the time series data in the simulated hemodynamics was altered. The point attractor, limit cycle attractor and bifurcation were observed by the increase of the time lag of the baroreflex system. And finally, deterministic chaos was observed in the simulation after the increase of the time lag.

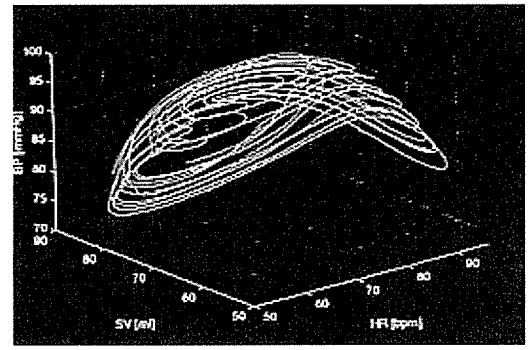

Fig. 2 Strange attractor of the deterministic chaos observed in the simulated time series data

Our results in this study suggested the importance on nonlinearity in the chaotic dynamics in the systemic circulation.

However, these results are the only the simulation, so, we must confirm this thesis in the actual living model. So, we moved to the animal experiments with artificial heart.

Artificial Heart with Baroreflex system

For the simulation of the baroreflex system, an artificial heart was used in this study.

By the use of an artificial heart complete prosthetic circulation independent from circulatory regulatory system was obtained.

In this study, we adopted the biventricular bypass type total artificial heart.

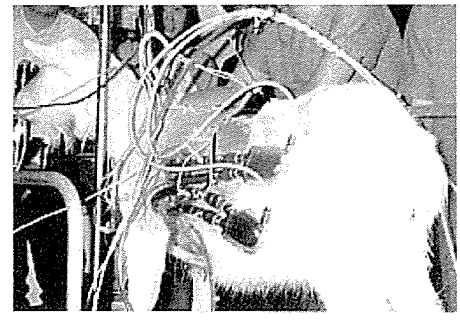

Fig.3 Animal experiment of the artificial heart with baroreflex system

We had invented the new artificial control algorithm named Resistance Based Adaptive Control system (RBAC) simulated the baroreflex system based on the 1/R control algorithm(5-7).

In this automatic control algorithm, optinal drive of the both pumps was automatically maintained. And in the second step, left and right heart outut balance was automatically controlled. Based on these two steps, artificial baroreflex system was added to these control logics based on the information of the peripheral vascular resistances.

As the results, chaotic time series data was observed in the animal experiments with artificial baroreflex system, though an only limit cycle attractor was observed in the time series during only optimal drive and L-R balance algorithm.

Our results in this experiment suggested the importance of the baroreflex system in the occurrence of the chaos in the time series data of the hemodynamic parameters.

Based on this result, we want to move to the clinical data

Clinical data of the patients with hypertension

There are a lot of drugs for the hypertension treatment. Several investigators noted that baroreflex sensitivity was improved by the use of the ACE inhibitor. In our study, baroreflex system plays an important role in the chaotic behavior in the hemodynamics. Baroreflex system is, of course, an important non linear dynamical factor in the circulatory regulatory system. So, it is interesting to evaluate the effect of baroreflex system in the non linear chaotic dynamics.

In 1975, Mandelbrot noted the thesis of FRACTAL. In this paper, Fractal structure was evaluated by the Dimension. This concept was expanded to the structure of the time series data, later.

Fractal dimension analysis was reported to be useful for the quantitative evaluation of the complex dynamics in non linearity.

In this study, fractal dimension analysis of the HRV was performed by the use of box counting method.

An example of a patient with hypertension was treated with ACE inhibitor and shown in a fig.4

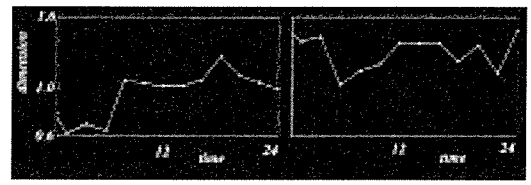

Fig.4 Circadian rhythm in the fractal dimension of the HRV in a patient with hypertension before and after the ACE inhibitor administration

In some patients with essential hypertension, sensitivity of the baroreflex system was reported to be tended to decrease. So, Information entropy of the complex dynamics may be thought to be decrease.

In this patient, fractal dimension of the HRV tended to decrease compared with normal subjects. After the administration of the ACE inhibitor, fractal dimension of HRV was recovered suggesting the improvement of the complex dynamics behavior.

In summary, baroreflex system may play an important role in the chaotic dynamical behavior in the hemodynamic parameters from the results of electrical circuit simulation non linear mathematical model, animal experiments of the artificial heart with baroreflex system and clinical data of a patient with essential hypertension.

Acknowledgements:

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EFFECT OF THE ALTERNATIVE MAGNETIC STIMULATION ON PERIPHERAL CIRCULATION FOR REGENERATIVE MEDICINE

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Abstract: The effect to peripheral circulation of alterative magnetic stimulation was evaluated in this study. The effect of magnetic stimulation as the medical treatment was examined using thermograph for healthy volunteers. The rise of skin temperature was observed by thermography as a result of the experiment, suggesting the improvement of peripheral circulation. Our results in this study may suggest the usefulness of the alternative magnetic stimulation on astherosclerosis.

Introduction

Recently, the Magnet therapy attracts attention as one of the alternative medicine in all over the world (1-3). However, there is very little quantitative research from a medical viewpoint. Recently, the medical treatment equipment by alternative magnetic stimulation was developed newly. The increase effect over a peripheral blood flow is expected and feasibility of the new regenerative medical treatment methodology may be embodied.

Magnetic medical treatment may be effective in the medical treatment of obstructive arteriosclerosis. We studied magnetic medical treatment by thermo graphy in this study.

Material and method

We experimented using 11 healthy men's volunteer. Approval of the Tohoku University medical department Ethics Committee was obtained. Informed consent was acquired with documents.

Firstly, thermography was recorded before the experiment. Thermography used in this experiment is NeoThermoTVS7000 of Nippon Avionics Co., Ltd. The temperature of both hands was recorded using this thermography.

After recording, a left arm of a volunteer put on the magnetic therapy machine, which can produce the alternative magnetic fields. Magnetic medical treatment machines are NStherapy and a Soken exchange magnetism medical treatment machine. Magnetic medical treatment for about 20 minutes was performed. Thermography measurement of both hands was performed after magnetic medical treatment.

Results

Significant side effects were not observed in all the cases of 11 examples. Completely safe magnetic therapy was possible in this experiment.

An example of the thermography after magnet therapy using alternative magnetic field is shown. in the figure.

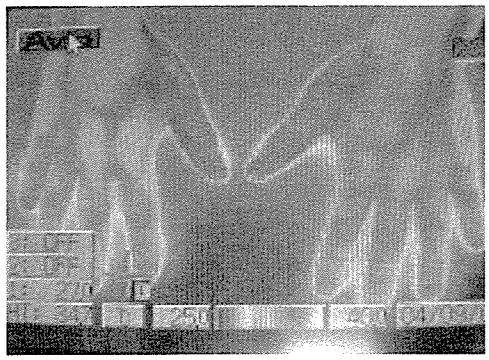

Fig.1 Thermograph after the alternative magnet stimulation for the left hand.

After the magnet therapy using alternative magnetic stimulation of the left hand, a left hand temperature is intentionally large compared with a right hand temperature.

Of 11 examples, there were many cases in which the temperature rise of thermography was shown, after magnetic medical treatment.

Discussion

Increase temperature suggested by the change of the thermography after the magnet therapy with alternative magnetic stimulation was observed in this study. The results of thermography may be data which suggest change of peripheral circulation.

The rise of skin temperature may mean an improvement of peripheral circulation. Therefore, magnet therapy with alternative magnetic stimulation may improve peripheral circulation. This phenomenon may be a impressions which suggests the possibility of the medical treatment to obstructive arteriosclerosis.

Alternative magnetic stimulation may generate feeble current in blood. Feeble current may influence the ion in blood. These are considered that it may affect autonomic nervous system and the peripheral circulation.

Recently, the angiogenesis by physical stimulus attracts attention in the medical fields. Especially alternative medicine and an angiogenesis are the topic of a medicine society. However, there are few papers which took notice of the physical stimulus by magnetism. The effect over peripheral circulation of a magnetic stimulus may be suggested from the result of this research.

We want to advance research also in the direction of an angiogenesis from now on.

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