Telemetry and Telestimulation via Implanted Devices Necessary in Long-Term Experiments Using Conscious Untethered Animals for the Development of New Medical Treatments

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SUMMARY Effective countermeasures against explosive increase in healthcare expenditures are urgently needed. A paradigm shift in healthcare is called for, and academics and governments worldwide are working hard on the application of information and communication technologies (ICT) as a feasible and effective measure for reducing medical cost. The more prevalent the disease and the easier disease outcome can be improved, the more efficient is medical ICT in reducing healthcare cost. Hypertension and diabetes mellitus are such examples. Chronic heart failure is another disease in which patients may benefit from ICT-based medical practice. It is conceivable that daily monitoring of hemodynamics together with appropriate treatments may obviate the expensive hospitalization. ICT potentially permit continuous monitoring with wearable or implantable medical devices. ICT may also help accelerate the development of new therapeutic devices. Traditionally effectiveness of treatments is sequentially examined by sacrificing a number of animals at a given time point. These inefficient and inaccurate methods can be replaced by applying ICT to the devices used in chronic animal experiments. These devices allow researchers to obtain biosignals and images from live animals without killing them. They include implantable telemetric devices, implantable telestimulation devices, and imaging devices. Implanted rather than wired monitoring and stimulation devices permit experiments to be conducted under even more physiological conditions, i.e., untethered, free-moving states. Wireless communication and ICT are indispensable technologies for the development of such telemetric and telestimulation devices.

key words: sustainable medical system, medical device, preclinical study, chronic disease, implantable device

1. Innovative Role of Information and Communication Technologies in Medical Practice

The primary goal of healthcare is to promote longer and healthier survival as well as better quality of life for the population; thus the healthcare industries may not be as profitable or as efficient as other industries. To make up for this, governments in most countries are involved in supporting healthcare provision for the people by means of public insurance systems, especially for those who cannot afford to pay for their own healthcare. Even though health promotion may ultimately help save human resources and productivity that may otherwise be lost to diseases, public insurance systems would, by definition, cost more than gain. As the population ages progressively and as medical practice involves increasingly more sophisticated procedures, the deficits continue to grow. The increase in medical expenditures is so great that this may account for a large proportion of the total national expenditures.

The governments of various countries take different approaches to address the healthcare problem, each government making continuous attempts to modify its existing healthcare model to make it work for the time being. The representative healthcare models include those of the United States, Europe, and Japan. Unfortunately, none of these models or their modifications is designed to be sustainable in the long term. The government of the United States tried to privatize medical insurance for as many people as possible, and the public insurance only covers the aged (Medicare) and low-income people (Medicaid). Unfortunately, this model yields a large (> 10%) uninsured population. The merit of private insurance is the freedom of selecting broader coverage of medical procedures by paying a higher premium. At the same time, this system limits the access to costly procedures for those people who cannot afford a high premium. Hence severe diseases necessitating expensive treatments may not be treated properly because the available healthcare depends on insurance coverage.

In Europe, conversely, a large public insurance system covers advanced treatments for the whole population, at the expense of a heavy tax burden. However, it is becoming difficult to adjust the system to more advanced treatments or to the aging population by simply imposing heavier taxes. Therefore, this public insurance system is also difficult to sustain in the near future. In Japan, the whole population is also covered by a statutory health insurance system, but the optional treatments available to the insured persons are considerably limited. One cannot opt to pay a higher premium to be covered for expensive treatments not approved under the universal coverage scheme. Such treatments can only be received on a private, self-paying basis. This system is also becoming difficult to sustain because of the increasing necessity (for medical reasons) and demands (for social reasons) to cover more advanced treatments.

Effective countermeasures against this explosive increase in healthcare expenditures are urgently needed. A paradigm shift in healthcare is called for, and the traditional healthcare delivery methods need to be reexamined. That is why academics and governments worldwide are working hard on the application of information and communication technologies (ICT) as a feasible and effective measure for reducing medical cost. The potential capability of ICT in re-

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duction medical cost and human resources are of paramount importance. At the same time medical ICT, once developed, should be put into practice without delay, so as to save the present medical insurance models in US, Europe, and Japan from bankruptcy.

2. Medical Device and Information and Communication Technologies

Clinical application of medical ICT requires the development of medical devices. Most medical ICT involve measurement or monitoring of biosignals, which can be achieved with sensors and wearable or implantable devices. Some medical ICT may also serve as a means of tele-diagnosis or tele-treatment under the supervision of medical professionals. Among various technologies, appropriate wireless communications between these devices as well as communication servers would be the key technology that contributes to reduce resources needed for patient management. Continuous real-time monitoring of pertinent biosignals is especially useful for the management of patients with more advanced stages of diseases. In such patients, prompt treatments in response to changes in biosignals or biosystem properties would prevent disease deterioration or repeated hospitalization. Even in stable patients, medical ICT may be useful in decreasing the frequency of visits to clinics.

As is discussed in the previous chapter, ICT-based medical practice is best applied to common diseases. The more prevalent the disease and the easier disease outcome can be improved, the more efficient medical ICT in reducing healthcare cost. Hypertension and diabetes mellitus are such examples. The former disease has been described as a “silent killer” because of its insidious onset and ultimate fatal outcome. The long-term outcomes of diabetes are also grave.

Chronic heart failure is another disease in which patients may benefit from ICT-based medical practice. Heart failure is a syndrome that manifests in the advanced stages of all heart diseases irrespective of the etiology. This syndrome is characterized by its progressive nature, high mortality rate, frequent and repeated need for hospitalization, and severely deteriorated quality of life. The potential aggravation of hemodynamics and cardiac function necessitates frequent visits to outpatient clinics or emergency rooms. Despite frequent hospital visits, hospitalization is often unavoidable. Once hospitalized, the quality of life of the patients is further worsened, and the costs for management increase dramatically. It is conceivable that daily monitoring of hemodynamics together with appropriate treatments may obviate the expensive hospitalization. ICT potentially permit continuous monitoring with wearable or implantable medical devices.

3. Pathways Needed for Approval of Medical Devices

Thorough and lengthy processes outlined below are required to obtain approval of medical devices. After prototyping the device, the same device that will be sold and manufactured in a GMP (good manufacturing practice)-certified production line should be tested in large animals. The safety and effectiveness (as defined for each device) should be proved statistically based on experimental data. The data should be obtained under GLP (good laboratory practice) standards (study conducted in an approved laboratory and using approved methods and devices) or equivalent to ensure the quality of data.

These preclinical (animal experiment) data are prerequisite for testing of the device in human volunteers. Clinical (human) studies can only be started after the preclinical data have been officially examined for whether they were obtained appropriately and whether they proved the safety and effectiveness of the device. This process should always be undertaken for any unapproved device and for any off-label use of an approved device. Clinical studies involving the use of an approved device for approved indications do not require the above process but they need the approval from the institutional review boards.

Therefore, the first step for the development of medical devices intended to realize the new ICT technology is to use it in animals to prove its usefulness. Even though the final data required for application to conduct clinical studies should normally be obtained from large animals, pilot studies may be performed in small animals.

4. Another Role of Information and Communication Technologies during Medical Device Development

As discussed in the previous chapter, medical ICT would reduce the medical costs most efficiently by combating the most common diseases such as hypertension and diabetes. These diseases are usually chronic in nature. Heart failure is also a chronic disease, affecting patients for years. The chronic nature of these diseases requires us to plan preclinical studies to observe the effectiveness of a new treatment for a certain period (this applies to both drugs and devices). In other words, we have to reproduce the equivalent chronic disease in animals and treat the disease similarly as in patients. This is also true for the development for the ICT-based medical devices.

Traditionally effectiveness of treatments is sequentially examined by sacrificing a number of animals (typically more than six to ensure statistical significance) at a given time point. Biosignals may be obtained under anesthesia just before euthanasia. Morphological and structural data are obtained directly by histological examinations. However, this type of approach has a number of limitations. To raise and to euthanize a large number of animals is a time-consuming process and is against the animal welfare. In addition, biosignals obtained under anesthesia are considerably different from those obtained in a conscious state. Histological examination provides precise but only static (still) images. Dynamic structural images can only be obtained when the animals are alive.

To circumvent these problems, physiological research
has also been devoted to methodological development for chronic animal experiments. Based on these results and by applying similar technologies of medical devices, several companies have begun to supply devices that can be used in chronic animal experiments. These devices allow researchers to obtain biosignals and images from live animals without killing them. They include implantable telemetric devices, implantable telestimulation devices, and imaging devices. Implanted rather than wired monitoring and stimulation devices permit experiments to be conducted under even more physiological conditions, i.e., untethered, free-moving states. Wireless communication and ICT are indispensable technologies for the development of such telemetric and telestimulation devices.

5. Examples of Chronic Animal Experiments Using Information and Communication Technologies

In this chapter, we would like to illustrate the importance of telemetry and telestimulation in the development of medical devices using two examples of animal experiments.

5.1 Improved Survival by Chronic Vagal Stimulation in Rats with Chronic Heart Failure after Healed Myocardial Infarction

As explained previously, patients with extensive or repeated myocardial infarction progress to chronic heart failure. Survival of these patients remains poor despite the development of various treatment modalities including drugs, medical devices, heart transplantation, and artificial hearts. Recently, medical devices have been highlighted due to their ability to prolong life beyond that can be achieved by drugs alone.

We have been developing a device-based treatment of heart failure by modifying the imbalance in autonomic tone. Excessive activation of sympathetic nerve and withdrawal of vagal nerve activity are known to play a causative role in aggravating heart failure. Drugs such as beta-adrenergic blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, which correct the sympathetic arm of the autonomic imbalance, prove to be beneficial. However, vagal tone enhancement has not been used successfully to treat chronic heart failure. Short-term electrical vagal nerve stimulation has been used only for the prevention of fatal arrhythmia during acute ischemia in animals. Therefore, we examined whether chronic (long-term) electrical vagal stimulation would delay the progression of heart failure and improve survival in rats with chronic heart failure after healed myocardial infarction [1]–[3].

Figure 1 illustrates the experimental setup (panels a and b) and study protocol (panel c). Each rat underwent two surgeries; in the first surgery we occluded the left coronary artery to create myocardial infarction, and in the second surgery we implanted telemetric and telestimulation devices. In the vagal stimulation group, we stimulated the right vagal nerve using bipolar electrodes (0.1–0.13 mA, 0.2 msec, 20 Hz-pulses) for 10 sec at intervals of 60 sec. This stimulation protocol was administered for 6 weeks. Using 24 rats, we compared the hemodynamics and histology between a group with and a group without vagal stimulation at the end of 6-week period. In another 52 rats, we conducted right vagal stimulation for 6 weeks and continued to keep these rats for a further 14 weeks to tabulate 20-week survival. Telemetry and telestimulation were essential to conduct this chronic experiment in conscious free-moving animals.

Compared to normal rats (serving as control), rats with heart failure had higher left ventricular filling pressure, lower contractility, and increased biventricular weight. With vagal stimulation, these changes (i.e., progression of heart failure) were partially improved (Fig. 2(a)). What is more important is that this novel treatment improved survival dramatically (Fig. 2(b)).

This novel treatment protocol has now reached the stage of being tested in a small number of patients [4]. De Ferrari et al. have developed an implantable vagal neurostimulator (Cardiofit, BioControl) and the device was tested in a pilot clinical study to obtain data for future approval. In 32 patients with heart failure (baseline ejection fraction ≤35%), the right vagal nerve was stimulated intermittently (4 mA, duty cycle 21%) for 6 months. The preliminary data indicated improved quality of life score (48 to 32, p < 0.01); increased 6-min walk distance (410 m to 471 m, p < 0.01), and increased left ventricular ejection fraction (23 to 27%, p < 0.01). More clinically relevant variables such as hospitalization frequency and survival will be investigated in a larger patient population.
Fig. 2 Effects of chronic vagal stimulation on remodeling and survival. ((a) and (b), reproduced with permission from [1])

(a) Left ventricular end-diastolic pressure (LVEDP, left), maximal rate of rise in left ventricular pressure (LV-dP/dtmax, middle), biventricular weight normalized by body weight (right) in normal control (C), no stimulation (Stim-) and vagal stimulation (Stim+) groups.

(b) Comparison of survival rates between Stim- group and Stim+ group

5.2 Precise Evaluation of Cardiovascular System Properties Needed to Combat Cardiovascular Diseases and Solve Circulatory Deconditioning during Space Flight

In establishing a rational treatment strategy, precise evaluation of the properties of key elements in the cardiovascular system is a prerequisite. Of these, knowledge of the properties of the left ventricle, which is the main source of energy to expel the blood, is particularly valuable. It is known that left ventricular properties are best expressed by the time-varying elastance curve. To obtain elastance we need to simultaneously measure high-fidelity pressure and volume waveform. A catheter-tipped micromanometer and a conductance volumetric method are frequently used for this purpose. The trial of chronic measurement of pressure-volume data is highly significant, as no one has ever measured the changes in ventricular properties during the lifelong course of hypertensive heart disease (a consequence of long-standing hypertension), and during the progression of heart failure.

We developed the prototype of an implantable pressure-volume telemetric device for this purpose [5], [6]. Figure 3 schematically illustrates the components of the device. It consists of a pressure-conductance catheter, an analog processor/transmitter, and a battery unit (panels a, d). In animals, the catheter is inserted into the left ventricle, typically from the apex. On the catheter, two sets of electrodes are affixed; in each set the outer pair serves as the excitation electrodes, and the inner pair as the recording electrodes. The set with wider inter-electrode distance is used to measure ventricular conductance, and the other set with narrower distance to measure blood resistivity (panels c, d). We applied 2 kHz- and 20 kHz-sinusoidal AC currents with known amplitude between excitation electrodes and measured the voltage amplitude to determine the conductance (Panel b). Online measurements of blood resistivity (using resistivity electrodes) and parallel conductance (using dual excitation frequency) permit continuous volumetry without any external maneuvers for calibration.

We used Bluetooth technology to transmit data from the implanted device to an external receiver (CASIRA, CSR, Cambridge, UK). The Bluetooth module (LMBTB027, Murata, Kyoto, Japan) was capable of transmitting 4 channel- (pressure, 2 kHz-conductance, 20 kHz-conductance, and electrocardiography), 200 Hz-, 16 bit-data in a real-time manner (data rate 12.8 kbps). For non-real-time analysis with high time resolution, we temporarily stored 2 kHz- signals in an SRAM (HM62 V16256, Hitachi, Tokyo, Japan) for 6 seconds and then transmitted data to the receiver.

Figure 4(a) is an example of left ventricular pressure and volume waveform measured in a rat by this telemetric device. As expected both pressure and volume decreased when the venous return to the left ventricle was decreased.

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In the receiver, the Bluetooth module transmitted the data to a personal computer, which was connected to the module via a USB interface. The data was processed using custom software written in MATLAB (The MathWorks, Natick, MA). The software performed real-time filtering and averaging to improve the signal-to-noise ratio.

We compared the data obtained by the implanted device with that obtained by an independent ultrasonic transit time flow probe (Fig. 4(b), flow waveform shown in Fig. 4(a)). In a representative rat, the pressure-volume loops obtained soon after implantation and at 6 days after implantation coincided well, as shown in Fig. 4(c).

We had difficulties in monitoring for longer than 2 weeks because of the fragility of the pressure transducers. Long-term stability of the pressure transducers that do not
require external calibration should be improved for chronic manometry. Notwithstanding this limitation, the development of this implantable telemetric device opens up the possibility of automatic tele-experiments. We have successfully performed a preliminary tele-experiment using an internet telecommunication line, intended for future space experiments. We can perform automatic but supervised experiments in a spaceship without any intervention by the spacecraft crew. This may help uncover the mechanism of circulatory deconditioning experienced during prolonged stay in microgravity in the near future.

6. Proposal for the Future Direction

Both engineers and clinicians should bear in mind that the benefit of the ICT-based medical system be examined in rather different ways than in conventional ways. The goal should not be just the better device or the better treatment. The primary goal should be set at reducing the cost, without aggravating or more preferably with improving the quality of medical practice (and ultimately the survival). The development of such system requires 1) low-cost, accurate, dependable methods for diagnosis and treatment even used by non-medical staff, 2) evidence (large clinical trial)-based algorithm to determine the optimal treatment, and 3) the accurate global evaluation of the impact on medical expenditures. Medical ICT should be developed with the continuous intimate interactions among engineers, clinicians, and the expert of the medical economics.

As discussed in Sect. 2, hypertension, diabetes, and chronic heart failure are three major candidates to combat with, using ICT-based medicine. How to reduce undetected and/or untreated hypertensive subjects together with improving drug compliance should be the first goal for hypertension. Effective measures to promote non-pharmacological treatments (i.e., diet, exercise, lifestyle modification, etc.) should be the first goal for diabetes and obesity. Development of more accurate methods to monitor daily changes in body weight, intake and output of water and salt would benefit the long-term management of heart failure.

7. Conclusion

Use of implantable devices combined with telemetry and telestimulation in unanesthetized and untethered animal models allows long-term observation of and intervention for pathologic changes during the course of common chronic diseases. More importantly, these devices can be used more efficiently for understanding disease mechanisms and rational development of novel treatments. These devices also provide the basis for automatic tele-experiments, even in the spaceship.

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References

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