The Effect of Donepezil Treatment on Cardiovascular Mortality

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The acetylcholinesterase inhibitor donepezil hydrochloride improves cognitive function in patients with Alzheimer's disease and vascular dementia. Given acetylcholine's important actions on the heart, we undertook a retrospective cohort investigation to assess whether donepezil usage affects cardiovascular mortality. In patients treated with donepezil, hazard ratios for total and cardiovascular mortality were 0.68 ($P = 0.045$, 95% confidence interval 0.46–0.99) and 0.54 ($P = 0.042$, 95% confidence interval 0.30–0.98), respectively. The apparent survival benefit in donepezil-treated patients should not be overinterpreted. Prospective clinical trials are warranted.

The acetylcholinesterase inhibitor donepezil hydrochloride improves cognitive function in patients with Alzheimer's disease and vascular dementia.[1,2] However, this agent also increases the availability of acetylcholine in peripheral tissues, including the heart, where it augments vagal influences on sinus node and cardiac conduction systems. Both sinus node function and conduction deteriorate with age.[3] Aging-associated changes in sinus node function may be related to calcium channel ($Ca_V1.2$) downregulation.[4] A reduction in the levels of connexin-43 expression (which is essential for electrical cell-to-cell stimulation) has been implicated in aging-associated deterioration of the conduction system.[5] Therefore, the elderly and very elderly are at particularly high risk for potentially life-threatening dysfunctions of the sinus node or conduction system. Augmented availability of acetylcholine in the heart through acetylcholinesterase inhibition could conceivably exacerbate the risk of bradycardia in this population. On the other hand, augmented acetylcholine could be beneficial, given the poor cardiovascular outcome in patients with diminished cardiac vagal activity.[6,7] Indeed, acetylcholinesterase inhibition appears to reduce overall mortality in patients with moderate to severe Alzheimer's disease[8] and Parkinson's disease–related dementia.[9] We conducted a retrospective cohort investigation to assess whether donepezil usage affects cardiovascular mortality in patients with Alzheimer's disease or vascular dementia.

RESULTS

We identified 1,004 patients with Alzheimer's disease and vascular dementia out of a total of 1,736 admissions. Donepezil was prescribed for 85 patients at the time of their discharge. Of those, 76 fulfilled all our inclusion and exclusion criteria. Of the 915 patients who did not receive donepezil, we randomly selected 80 patients matched for age, sex, and race to serve as the control group (**Table 1**). The majority of the patients enrolled had Alzheimer's disease. The main reasons for hospital admissions were respiratory symptoms (28%) in donepezil-treated patients and orthopedic (15%) and cardiac causes (15%) in untreated patients.

Over a mean follow-up period of 29 ± 17 months in donepezil-treated patients and 28 ± 25 months in untreated patients, we identified 115 fatal events. Of these, 88 were available in the medical records and were successfully matched to the Tennessee death-certificate database. In 27 patients, fatal events were determined solely from this database. Fatal cardiovascular events occurred in 36 donepezil-treated and 18 untreated patients ($P < 0.01$). Cox proportional hazard regression analysis showed that, relative to the untreated group, donepezil-treated patients had lower total mortality risk and also lower cardiovascular mortality risk (after adjusting for potential confounders such as vascular dementia, age, sex, and ethnicity) (**Table 2**). Additionally, Kaplan–Meier survival analysis showed better overall and cardiovascular survival in donepezil-treated patients in the first 3–4 years of follow-up (**Figure 1**). The intergroup difference disappeared after 4–5 years, probably because of the small number of surviving patients.

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Table 1 Characteristics of the patient population studied

Characteristic	DPZ$^+$ (%) $n = 76$	DPZ$^-$ (%) $n = 80$
Follow-up time (months)[a]	29 ± 17	28 ± 25
Age[a]	80 ± 8	81 ± 8
Sex		
Female	51 (67.1)	54 (67.5)
Male	29 (38.2)	26 (32.5)
Race		
White	63 (82.9)	56 (70)
Nonwhite	17 (22.4)	24 (30)
Diagnosis		
Alzheimer's disease	67 (88.2)	64 (80)
Vascular dementia	9 (11.8)	16 (20)
Chief complaint at time of admission		
Orthopedic	13 (17.1)	12 (15)
Metabolic or nutritional	7 (9.2)	8 (10)
Cerebrovascular event	2 (2.6)	5 (6.3)
Other central nervous system disease	5 (6.6)	5 (6.3)
Cardiac event	14 (18.4)	12 (15)
Respiratory	21 (27.6)	10 (12.5)
GI tract	5 (6.6)	8 (10)

DPZ, donepezil; DPZ$^+$, those who received donepezil medication; DPZ$^-$, those who did not receive donepezil medication; GI, gastrointestinal.

[a]Values are expressed as means ± SDs.

Table 2 Multivariate analysis of hazard ratios for fatal cardiovascular events and all fatal events

	Fatal CV events		All fatal events	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Donepezil medication	0.54 (0.30–0.98)	0.042	0.68 (0.46–0.99)	0.045
Vascular dementia	1.43 (0.69–2.99)	0.338	1.35 (0.82–2.21)	0.234
Age	1.03 (0.99–1.07)	0.095	1.02 (0.99–1.04)	0.151
Male	1.83 (1.03–3.23)	0.038	1.43 (0.97–2.12)	0.071
Nonwhite	1.40 (0.78–2.53)	0.261	1.30 (0.86–1.97)	0.212

CI, confidence interval; CV, cardiovascular.

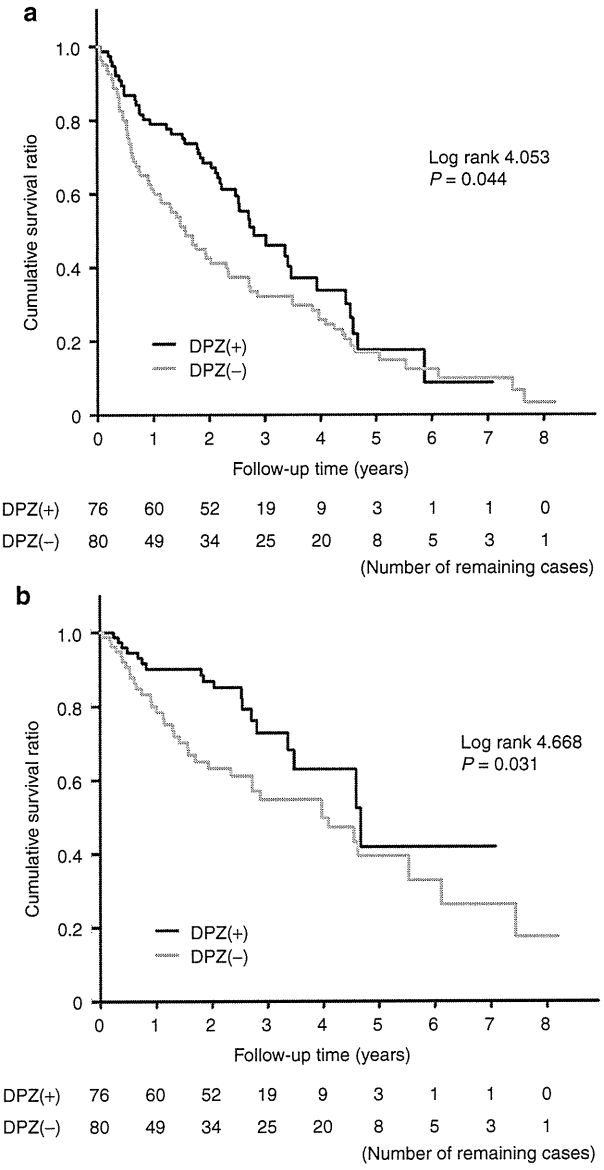

Figure 1 Kaplan–Meier survival curves for (**a**) all fatal events and (**b**) cardiovascular deaths. DPZ, donepezil.

DISCUSSION

Given donepezil's mechanism of action and the high risk for sinus node dysfunction or cardiac conduction impairment in patients receiving the drug, we were concerned that there could be an increase in fatal cardiovascular events in donepezil-treated patients. Instead, our retrospective analysis showed better cardiovascular and overall survival in donepezil-treated patients. Our study has several important limitations and must be interpreted with caution. First, the numbers of patients, both donepezil-treated and untreated, were relatively low. Second, although both groups were carefully matched, a bias such as physicians' decisions on discharge prescriptions could not be eliminated because all the data were retrospectively collected from hospital discharge summaries. Finally, although recent clinical studies demonstrated that donepezil is well tolerated,[2] we have no information concerning medication compliance in our study. Despite these limitations, we believe that our analysis contains clinically relevant information that deserves to be addressed in prospective studies.

Theoretically, donepezil could affect the functioning of the sinus node and cardiac conduction systems through central nervous and peripheral mechanisms. Donepezil has previously been shown to raise brain acetylcholine availability.[10] Central cholinergic stimulation could raise blood pressure through the release of vasopressin[11] and the activation of the sympathoadrenal system.[12] Baroreflex-mediated bradycardia could occur. More likely, acetylcholinesterase inhibition could induce bradycardia through actions on cardiac muscarinic

receptors, as has been shown in rats[11] and in human subjects.[13] However, whether or not donepezil raises heart rate variability, which is strongly influenced by vagal influences on the sinus node, is controversial.[14,15] Previous studies suggested that vagal heart rate control may be impaired in patients with Alzheimer's disease.[16,17] It is possible that such impairment in vagal function could have decreased the likelihood of life-threatening bradycardia in the patients in our study.

Potentially favorable prognostic influences of donepezil may not be confined solely to improvement in cognitive function.[18,19] For instance, tacrine, another cholinesterase inhibitor, did not alter life expectancy in spite of beneficial actions on cognitive and global function.[20] It is possible that augmented vagal function contributes to the survival benefit seen with donepezil. For example, chronic electrical stimulation of the vagus nerve improved long-term survival in rats with congestive heart failure after a large myocardial infarction.[21] Recent studies suggest that acetylcholine from vagal stimulation protects cardiomyocytes from acute hypoxia and ischemia, in part through hypoxia-inducible factor-1α.[22] Moreover, the antiarrhythmia effect of vagal stimulation was accompanied by preservation of phosphorylated connexin-43 protein.[23] Cholinesterase inhibition reduced the levels of thrombomodulin and β-thromboglobulin, which are markers of endothelial and platelet activation, respectively.[24] Finally, donepezil might have a role in direct stimulation of acetylcholine synthesis in cardiomyocytes through mechanisms other than acetylcholinesterase inhibition.[25]

In conclusion, our retrospective cohort study showed that donepezil was associated with reduced cardiovascular mortality in patients with Alzheimer's disease or vascular dementia. Given the limitations of our study, the apparent survival benefit in donepezil-treated patients should not be overinterpreted. However, our observations, as well as data from previous studies suggesting that improved survival is associated with acetylcholinesterase inhibition,[8,26–28] should be scrutinized in mechanistic studies and in larger clinical trials. In particular, we suggest investigating in greater detail the action of donepezil on the cardiovascular system in patients with Alzheimer's disease or vascular dementia. Prospective studies for a duration of several years may be required to gauge the overall risks and benefits of donepezil treatment in this vulnerable population.

Table 3 Outcomes in patients who received donepezil treatment and in those who did not

	DPZ^+ (%)	DPZ^- (%)
Survivors	31 (40.8)*	10 (12.5)
Hospital admissions for cardiac events	10 (13.2)	17 (21.3)
Fatal CV events	18 (23.7)*	36 (45.0)
Ischemic heart disease	9 (11.8)	16 (20)
Other heart disease	5 (6.6)	12 (15)
Cerebrovascular diseases	8 (10.5)	4 (5)
Fatal non-CV events	27 (35.5)	34 (43.0)
Neoplasm	2 (2.6)*	14 (17.5)
Malignant solid neoplasm	2 (2.6)	5 (6.3)
Malignant, hematology, and lymph system	0 (0)	3 (3.8)
Malignant unknown neoplasm	0 (0)	6 (7.5)
Metabolic or nutrition	1 (1.3)	4 (5)
Diabetes mellitus	1 (1.3)	1 (1.3)
Lipid disorder	0 (0)	1 (1.3)
Volume depletion	0 (0)	2 (2.5)
Central nervous system	19 (25)*	7 (8.8)
Parkinson's disease	1 (1.3)	0 (0)
Alzheimer's disease	13 (17.1)	5 (6.3)
Unspecified dementia	4 (5.3)	2 (2.5)
Encephalopathy	1 (1.3)	0 (0)
Respiratory system	4 (5.3)	4 (5.0)
Pneumonia	2 (2.6)	3 (3.8)
Other chronic lower respiratory disease	2 (2.6)	0 (0)
Chronic obstructive pulmonary disease	0 (0)	1 (1.3)
Digestive system	0 (0)	4 (5)
Liver disease	0 (0)	2 (2.5)
GI bleeding	0 (0)	1 (1.3)
Cardiac disease	0 (0)	1 (1.3)
Renal system	1 (1.3)	0 (0)
Urinary tract infection	1 (1.3)	0 (0)
Other	0 (0)	1 (1.3)
Complications of medical and surgical care	0 (0)	1 (1.3)

CV, cardiovascular; DPZ, donepezil; DPZ^+, those who received donepezil medication; DPZ^-, those who did not receive donepezil medication; GI, gastrointestinal.

*$P < 0.01$ for comparisons between the DPZ^+ and DPZ^- groups.

METHODS

The institutional review board of Vanderbilt University and the Tennessee Department of Health approved the study protocol.

Data source. We retrospectively obtained data from the Hospital Discharge Data System database of Tennessee, the Vanderbilt Hospital medical record database (StarPanel), and the Tennessee death-certificate database (Tennessee Department of Health Death Data System Manual 2004, Bureau of Health Informatics, Office of Health Statistics). To protect the privacy of the subjects, we removed all traceable, person-specific identifying information from the data set created by linking subjects across the three data sources. Each subject was assigned an anonymous, coded study number.

Patient selection. We included patients with Alzheimer's disease or vascular dementia admitted to Vanderbilt Hospital between 1 January 1997 and 31 December 2003. The clinical diagnosis of probable Alzheimer's disease or vascular dementia was determined by the attending physicians on the basis of the complete medical history, neurological examination, blood chemistry, and computed tomography of the brain. We excluded patients who had a follow-up period of <14 days. The patients had to be Tennessee residents because we relied on the state's death-certificate database. We identified donepezil-treated patients and compared their outcomes with those of randomly selected patients, matched for age, sex, and ethnicity, who had not been treated with donepezil.

Patient characteristics and outcomes. Via the Vanderbilt Medical Center record database (StarPanel), we acquired information on patients' age, sex, ethnicity, residence, dementia diagnosis, chief complaint at admission, past medical history, prognosis, cardiovascular events, and fatal events. Dates and causes of death were identified from the Tennessee

death-certificate database (Tennessee Department of Health Death Data System Manual 2004, Bureau of Health Informatics, Office of Health Statistics) up to 31 December 2005. Patients who survived up to the time of discharge from the hospital and whose names were not found in the death-certificate database up to the cutoff date were considered to be alive as of that date. We use the major code of the Tennessee death-certificate database for demographic description and analysis of data for patients who had fatal events. The causes of death were organized in subclasses as shown in Table 3. The primary end point was a fatal cardiovascular event. The secondary end point was occurrence of any fatal event. Cardiac events experienced by the patients, including acute coronary syndrome or decompensated heart failure at the time of admission to Vanderbilt Hospital, were investigated. Furthermore, any cardiovascular event for which patients were admitted to the Vanderbilt cardiac unit during the follow-up period was also investigated.

Statistical analysis. Demographic distributions and clinical characteristics were determined for subjects who were prescribed donepezil (DPZ^+ group) and for those who were not (DPZ^- group). Data are presented as mean ± SD for continuous variables and as frequencies for categorical variables. Comparisons between the two groups were performed using Mann–Whitney *U*-tests. The Pearson χ^2-test was used for categorical variables. Overall patient survival was analyzed using a Cox proportional hazards model to control for covariates. Cox proportional hazards regression models were applied to compare survival rates in the DPZ^+ and DPZ^- patients at the time of discharge from the hospital. The models were adjusted for the effect of independent mortality risk factors including vascular dementia, age, sex, and race. Kaplan–Meier survival curves were constructed to assess the probability of survival free from all fatal events and cardiovascular fatal events. The differences were tested using the log-rank test. A two-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, IL).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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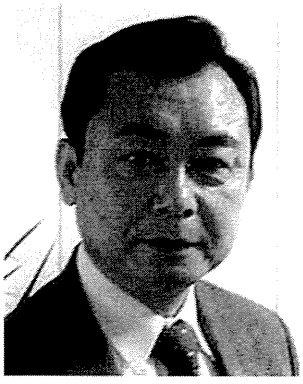
In the Spotlight: BioInstrumentation



Ken-ichi Yamakoshi, *Member, IEEE*

I. Introduction

OVER recent decades a very large number of studies have been vigorously carried out to develop invasive and non-invasive physiological measurement bioinstrumentation, for use in areas such as basic and clinical medicine, healthcare and welfare science, sports science, and others. Noninvasive measurement is generally considered to be the most desirable approach for practical use, but in addition there is a significant increasing need to monitor physiological variables in a manner that allows the subject to be unconstrained, which can be achieved by the so-called ambulatory or wearable monitoring techniques. This means that biological sensors and/or miniaturized measuring units are to be carried by the subject or are to be embedded in his/her clothes. The development of such monitoring approaches through modern technological advances has progressed remarkably, and this review briefly introduces several areas where such recent advances have been made.

II. Ambulatory/Wearable Physiological Monitoring

As is well recognised, the first attempts to develop a portable ECG device with radio telemetry, called "*Radioelectrocardiography*" [1], and then with tape recording [2] were reported by N. J. Holter. Refinements of such systems are now commercially available and widely used in clinics as the Holter ECG recorder [see [3]]. Following Holter's epoch-making initiative, numerous research studies have been carried out aiming to monitor a wide range of physiological variables during ambulatory use. In particular, a portable sphygmomanometer, the "ambulatory blood pressure monitor (ABPM)" [4], [5], which is based on the auscultation and/or cuff-oscillometric method [6], has been one successful example akin to the Holter ECG recorder, and these two are now widely used in clinical medicine as key devices. Also, modern micro-electronics and mechanical technologies have enabled us to produce more compact and convenient devices for home use.

Fig. 1 shows the basic construction of a typical ambulatory/wearable monitoring system, consisting of a biological sensing unit (BSU), a portable measuring unit (PMU) for signal processing and data storage, and a data reproducing and display unit (DRU), which is usually a conventional personal computer (PC). The BSU and the PMU are carried by the subject, and in the BSU are either conventional biological sensors/electrodes or sensing devices embedded into the subject's clothes. For signal processing and data storage in the PMU, a microcomputer-based system is usually adopted at present to make it more compact and convenient to operate. Over the last decade advances in information and communication technologies have led to the use of wireless communications between BSU and PMU and between PMU and DRU.

A selection of recent attempts at physiological monitoring relating in particular to cardio-pulmonary, human activity and biochemical information are now briefly described.

A. Cardio-Pulmonary Monitoring

Due to the importance of evaluating cardiovascular and pulmonary function there have been many attempts over the past several decades to develop appropriate ambulatory/wearable physiological measurement systems. These have been based on key physiological variables, including the ECG, blood pressure (BP) and respiration.

Considerable improvements as compared with the initial Holter ECG recorder have been made in terms of miniaturization and data storage in the PMU and regarding data communications. In addition, much effort has been given to improving the design and fabrication of ECG electrodes. Wet-gelled spot

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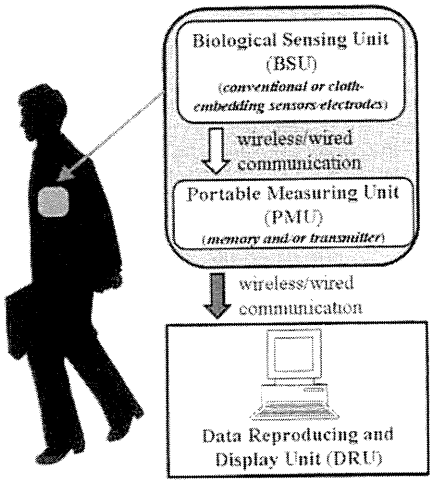

Fig. 1. Outline of basic construction of ambulatory/wearable monitoring system. The system mainly consists of a biological sensing unit (BSU), a portable measuring unit (PMU) and a data reproducing and display unit (DRU). See text for further explanation.

electrodes remain the most common approach, but efforts continue to be made to improve dry electrode designs as such an electrode is thought by some workers to offer good prospects of achieving long-term electrical stability for ambulatory use. As previously reviewed in this Spotlight column [7], [8], several approaches to measure ECG using dry electrodes have been introduced, although further improvements of the electrical characteristics were still required. Recently Gargiulo *et al.* [9] have reported an approach based on the use of conductive rubber electrodes together with an ultra-high input impedance ECG amplifier and, with Bluetooth wireless communication, have demonstrated 24 hours successful ECG monitoring. It is interesting to note that their system was actually applied to the measurement of the ECG during body-building and swimming exercises and they also claimed its usefulness to prevent an athlete's sudden death due to a syndrome called "athlete's heart" [10], [11].

An interesting approach to monitoring such vital signs as ECG and respiration was implemented within the WEALTHY project [12], [13], supported by the 5th Framework IST (Information Science and Technology) Programme of the European Union. In this research woven sensors that could be worn without any discomfort for the user were developed. The fabric sensors were woven from smart fibres and yarn having conducting and piezoresistive properties. These were formed and integrated into well-fitting garments and then used to obtain recordings of vital signs. It is reported that the system can provide reliable and satisfactory data as compared with conventional standard methods. It was also reported that the proposed system could assist patients during rehabilitation training or subjects working in extremely stressful environmental conditions, ensuring continuous surveillance.

There have been several recent attempts to use textile electrodes as wearable sensors. Mitchell *et al.* [14] devised a t-shirt embedding a textile-based piezoresisistive sensor together with a Zigbee wireless transmitter for the monitoring of breathing. Wireless communication was made between the sensor and a PC installed in a Zigbee receiver, where the respiration signal was displayed in real-time to present to a subject for breathing exercises. It is stated that this wireless biofeedback system could be useful for breathing training that is a part of the treatment for respiratory illnesses such as cystic fibrosis.

Just recently, Rantala *et al.* [15] designed an interesting wearable optical sensor sewn into clothing for the ambulatory monitoring of respiration and tidal volume. The sensor has 16 specially aligned optical fibres. The intensity of light passing through the fibres changes in response to fibre bending due to respiration and a signal representing changes in tidal volume is thereby obtained.

Photoelectric plethysmography is also promising as a convenient means for ambulatory use. As an interesting healthcare application, Fletcher *et al.* [16] developed a wearable photoplethysmographic sensor with wireless networking to monitor photo-pulsations. This is combined with a sensor for measuring electrodermal activity (EDA) from the wrist designed by Poh *et al.* [17], to evaluate autonomic nervous activity. They proposed two types of network systems; one was with IEEE 802.15.4 so as to apply multiple sensors and the other with Bluetooth to communicate directly with a mobile phone.

In contrast to these vital signs that can be monitored with relative ease, arterial blood pressure (BP) and cardiac output (CO) are the essential parameters for the detailed evaluation of cardiovascular haemodynamic functions. Through a considerable amount of research and development activity and effort, the ABPM has become one of the most successful examples of the commercialization of research outcome. This device is quite convenient for practical use, measuring BP at a set interval of 30 min or more. However, this means that it can acquire less than 48 data points per day [18], [19]. Because there are approximately 80,000–100,000 BP data points per day produced by individual cardiac beats, only about 0.05% of the complete BP data set can be obtained by ABPM. It is therefore desirable to acquire BP on a beat-by-beat basis. It is furthermore apparent that the acquisition of BP and CO data together on a beat-by-beat basis combined with other cardiovascular data would be much more powerful. For example, this could enable the detailed analysis of haemodynamic responses and autonomic regulation of the cardiovascular system to be carried out in response to various stressful daily activities.

With this as a background, the author's group has recently developed a new beat-by-beat cardiovascular haemodynamic monitoring system both for ambulatory and/or stationary use [20] on the basis of a technological combination of the volume-compensation [18], [19], [21] and transthoracic electrical admittance methods [18], [19], [22]–[24]. Recently, Ogawa *et al.* [25] have applied this system to the assessment of cardiovascular stress reaction on a beat-by-beat basis in response to daily activities using the recently proposed Gregg's method [26]. They clearly demonstrated the separation of active, passive and mixed stress coping during daily living.

B. Activity Monitoring

The importance of ambulatory activity monitoring is well recognized in the fields of gerontology, rehabilitation, exercise training and general healthcare. In the field of rehabilitation, for

example, a therapist must evaluate motion characteristics, for example during standing up, walking, and other activities. However, it is very much a situation in which the therapist must usually make assessments subjectively by direct observation and quantitative assessment of activities is highly desirable. One method employed is to make recordings using a three-dimensional motion capture system, but the range over which such recording is possible is usually limited and data analysis is complicated, rendering this system unsuitable for use in practical rehabilitation.

Some wearable instruments capable of monitoring activity [27]–[32] and gait and posture [33], [34] using sensors such as an accelerometers, a gyro-sensors and so on, have been developed. One such development has been reported by Motoi *et al.* [35], and this enables the monitoring of static and dynamic posture changes in the sagittal plane together with gait and walking speed. The system uses three miniaturized units fixed to the trunk, thigh and calf and it measures their angles with respect to the gravitational direction using accelerometers and gyro-sensors. Each unit has these sensors as well as a Zigbee transmitter for wireless communication for real-time observation and a micro-SD card for long-term recording. The authors successfully demonstrated the viability of this system for the quantitative evaluation of the efficacy of rehabilitation programs as well as normal daily activities.

Another noteworthy attempt aimed at exercise training is reported by Lee *et al.* [36]. This system is capable of monitoring activity along with the ECG using a tri-axial accelerometer and conductive fabric electrodes embedded in a shirt. This sensing unit is networked with IEEE 802.15.4 Zigbee W-PAN (wireless personal area network). It is noted that this type of sensing network could be promising for many kinds of data acquisition by retrofitting a large number of miniaturized sensors.

C. Biochemical Monitoring

To date, numerous developments have been focused on physiological monitoring relating to cardio-pulmonary and activity information as mentioned above. However, there have been few attempts to monitor biochemical quantities for ambulatory use, despite its usefulness and importance to evaluate biochemical status for healthcare management. In this context, Yang *et al.* [37] recently attempted to fabricate a biosensor directly printed on underwear, similar to a screen-printing process onto the textile substrate. The authors described the detection of 0–3 mM ferrocyanide, 0–25 mM hydrogen peroxide and 0–100 M NADH. It is also noteworthy that the European Union project called "BIOTEX" developed biochemical-sensing techniques using a textile-based wearable biosensor to monitor pH and sodium (Na^+) in sweat [38]–[40]. Here, the sensing part consists of (1) a passive fabric pump made of a super absorbent material for the continuous suction of sweat from the skin, (2) a pH sensitive dye, and (3) an LED/photodetector pair to measure color changes of the dye due to the changes of the solute concentration in sweat. They also used a pair of gold electrodes and ion-sensitive membrane as the wearable sodium sensor.

III. Future Aspects

Recent developments and the present status of non-invasive and ambulatory/wearable monitoring were briefly introduced in this review. In the light of the growth of the aging society worldwide, such monitoring techniques will be increasingly required as a possible scheme for preventive medicine, early diagnosis, rehabilitation and sports medicine, as well as timely treatment of lifestyle-related diseases.

Several research approaches described herein appear innovative and groundbreaking, particularly in the developments of instrumented garment systems and wireless communication techniques with miniaturized sensors. Optimistically it might be anticipated that such convenient instruments could be made available at reasonable costs in the future, although there are still numerous challenging obstacles to be addressed, such as the rather conflicting needs for small size, wear comfort, simplicity of operating procedures, accuracy, power management, stability and so on for truly practical use.

Taking the availability and potential of these techniques to contribute in many biomedical fields into consideration, further comprehensive studies will still be required to realize this potential and thereby achieve an advanced and truly practical approach. Nevertheless, the considerable recent dramatic advances in microelectronic, micromechanical, information and communication technologies will doubtless resolve the problematic issues that still remain.

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Evaluation of Cardiovascular Stress Reaction Using HPCD Method on a Beat-by-beat Basis[1]

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Abstract: In order to establish a bionic model/system in cardiovascular fields, comprehension of hemodynamics is important. In this study, a novel beat-by-beat hemodynamic system evaluation method named "beat-by-beat HPCD method" is proposed and evaluated. Gregg's theoretically driven model of hemodynamics which was called "HPCD method" is improved by using non-invasive and beat-by-beat cardiovascular measurement of mean blood pressure and cardiac output.

Continuous beat-by-beat measurements of MBP and CO were done on three healthy male subjects during three hours. In the measurement, a five minutes cold pressor test was executed in each subject and also each subject did exercise using a bicycle ergometer in five minutes and walked during 15 minutes. Measured beat-by-beat MBP and CO can derive beat-by-beat HP (hemodynamic profile) and CD (compensation deficit). Then, beat-by-beat changes clearly observed from plots on HP axis and CD axis plane. More vascular response can be observed on cold pressor and more myocardial response can be observed on ergometer exercise. During walking period, the response is intermediate between cold pressor and ergometer exercise. Finally, the proposed method can be considered as applicable to evaluate cardiovascular bionic system especially on evaluation of a person being subjected to stress.

Keywords: hemodynamics; stress; cardiovascular system; hemodynamic profile and compensation deficit model

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INTRODUCTION

In order to establish a bionic model/system in cardiovascular fields, comprehension of hemodynamics should be considered as important. In this study, a novel beat-by-beat hemodynamic system evaluation method named "beat-by-beat HPCD method" is proposed and evaluations of human hemodynamic status in three different stress loading status were attempted using the method.

MATERIALS AND METHODS

As known, there have been many attempts of measurement and/or estimating for hemodynamic parameters. Among them, Gregg et al. recently proposed a new theoretically driven model of hemodynamics and demonstrated its application for hemodynamic parameters (Gregg et al., 2002) which were called "HPCD method." The "HPCD method" is based on cardiac output (CO) and total peripheral resistance (TPR). Though it is not possible to measure TPR directly, TPR can be estimated from CO and mean blood pressure (MBP) as Eq. (1), as shown in Fig. 1.

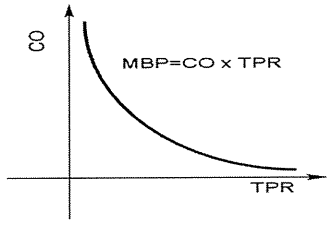

Figure 1: Three hemodymanic parameters; mean blood pressure (MBP), cardiac output (CO) and total peripheral resistance (TPR)

$$MBP = TPR * CO \quad (1)$$

The baseline measurement gives MBP and CO on baseline MBPb and COb, giving TPR on baseline TPRb as Eq. (2).

$$MBPb = TPRb * COb \quad (2)$$

Dividing Eq. (1) by Eq. (2) gives Eq. (3a) as below.

$$MBP/MBPb = TPR/TPRb * CO/COb \quad (3a)$$

Eq. (3a) means relative reactivity of three homodynamic parameters, then the three terms of Eq. (3a) are expressed as MBPr, TPRr and COr (shown as Eq.(3b)).

$$MBPr = TPRr * COr \quad (3b)$$

Then, logarithm of Eq. (3a) gives Eq. (4) of additive synthesis.

$$log(MBPr) = log(TPRr) + log(Cor) \quad (4)$$

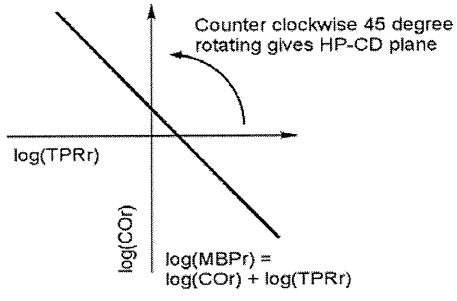

Figure 2: Hemodinamic parameters on orthogonal dimension consisted of logarithm of TPR and CO

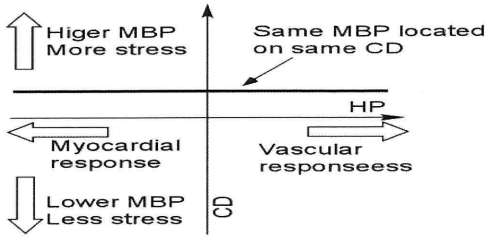

Figure 3: HP-CD plane: HP means "hemodynamic profile" and CD means "compensation deficit"

Now, Eq. (4) means orthogonal dimensions consisted of logarithm of TPR and CO as shown in Fig. 2. Finally, counter clockwise 45 degree rotating of this log-TPR axis and log-CO axis plane gives a new orthogonal dimensions consisted of logarithm of TPR and CO "hemodynamic profile (HP)" axis and "compensation deficit (CD)" axis, and the HP-CD plane can have information relating reactivity of hemodynamic parameters. In the HP-CD plane, CD axis gives relative stress reaction information and HP axis gives information of relative myocardial-and-vascular balance, as shown in Fig. 3.

Gregg et al. applied their method to evaluate hemodynamic status of human only intermittently. Consequently, their method remained one-shot evaluation and comparison of different hemodynamic statuses; i.e. comparison of before and after a stress loading. Meanwhile, we have been developed beat-by-beat continuous and non-invasive measurement methods and systems of cardiovascular/hemodynamic parameters that can measure blood pressure and cardiac output continuously (Nakagawara & Yamakoshi, 2000) whose measurement methodologies are based on volume-compensation method (Yamakoshi et al., 1979 & 1980) and transthoracic admittance plethysmograph method (Ito et al., 1976). Here, we thought inevitably that Gregg's HPCD method can be enhanced to beat-by-beat evaluation of hemodynamic by combining with our beat-by-beat measurement system.

Continuous beat-by-beat measurements of MBP and CO were done on three healthy male subjects (yrs. 21-23) during three hours. In the measurement, a five minutes cold pressor test was executed in each subject and also each subject done exercise using a bicycle ergometer in five minutes and walked during 15 minutes. For obtaining a baseline of the physilogogcal measurement, each subject was placed supine position in the first 5 minutes of the measurement. The cold pressor test is considered inducing mainly myocardial response and exercise using an ergometer is considered inducing mainly vascular response.

Continuous beat-by-beat hemodynamic measurement provides continuous plots on HP-CD plane. For evaluate distribution of those plots, principal component analysis (PCA) based evaluation is applied. In this paper, representative parameter of distributed plots is defined as an ellipse that drawn with PCA: That representative ellipse is drawn as follows (illustrated as Fig. 4):

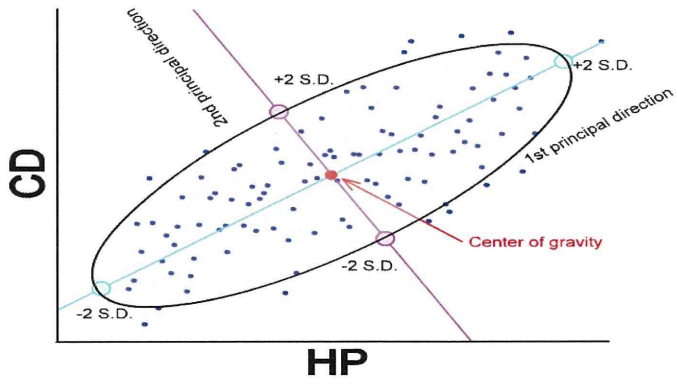

Figure 4: How to draw representative ellipse of plots on HP-CD plane

1. PCA is applied the plots then obtaining the 1st and 2nd principal direction.
2. The center of the ellipse is defined as the center of gravity the plot.
3. The long axis of the ellipse is defined as ±2 S.D. of the 1st principal component score.
4. The short axis of the ellipse is defined as ±2 S.D. of the 2nd principal component score.

RESULTS AND DISCUSSION

Measured beat-by-beat MBP and CO can derive beat-by-beat HP (hemodynamic profile) and CO (compensation deficit). Then, beat-by-beat changes clearly observed from plots on HP axis and CD axis plane. In cold pressor phase, the plots on HP-CD plane move to more vascular direction. In contrast, the plots move to more myocardial direction in ergometer exercise. In waking period, the plots distributed on the area between cold pressor phase and ergometer exercise phase. An example of the plots and representative ellipses of each status are shown in Fig. 5. This suggests that cardiovascular reactions of stress on daily living as walking should be considered as mixed myocardial and vascular response. This must mean that same blood pressure response can be originated from different hemodynamic status. Then, the proposed method can be considered as applicable to evaluate cardiovascular bionic system in a dynamic sense, on a beat-by-beat base. For a future cardiovascular bionic system analysis/synthesis, the view of myocardial-and-vascular balance should be important.

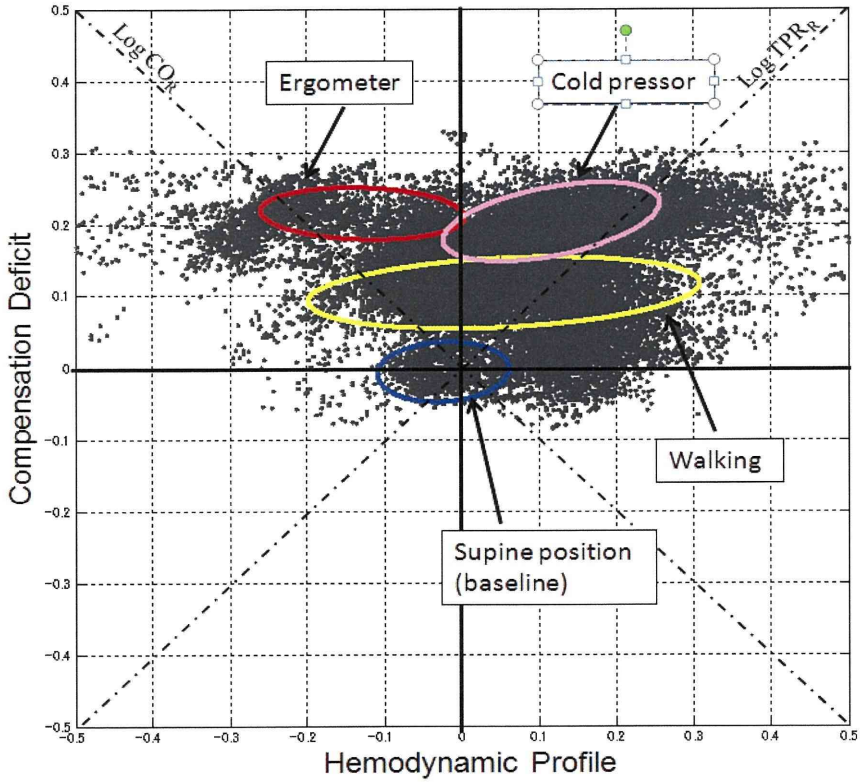

Figure 5: An example of beat-by-beat measurement based HP-CD plot and its evaluation. Gray dots are beat-by-beat plot of hemodynamic parameter, HP and CD. The blue ellipse shows distribution on supine position. The red, pink and yellow ellipses show cold pressor, ergometer exercise and walking respectively

CONCLUSION

Beat-by-beat HPCD hemodynamic evaluation method that was combination of Gregg's HPCD method and our beat-by-beat cardiovascular measurement was proposed and attempted. By the method, stress reactions can be observed clearly.

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Current Status of Noninvasive Bioinstrumentation for Healthcare

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Key words: noninvasive ubiquitous healthcare monitoring, ambulatory/wearable physiological monitoring, nonconscious physiological monitoring, medical crisis, preventive medicine, early diagnosis and treatment

In the so-called "super-aging society," noninvasive healthcare monitoring has been increasingly required as a possible scheme for preventive medicine, early diagnosis, and timely treatment of lifestyle-related diseases. As contributions towards the development of the most desirable aim of achieving ubiquitous healthcare monitoring, two promising systems, "ambulatory or wearable physiological monitoring" and "nonconscious physiological monitoring," which have recently been developed through modern technological advances, are introduced in this paper. Each of these two monitoring techniques appears to have the potential to contribute to the fields of personal healthcare, medical care, and rehabilitation among others. Nevertheless, further comprehensive studies will still be required to realize this potential and thereby achieve an advanced and truly practical approach. This is also discussed in this paper.

1. Introduction

In modern society, humankind has been confronted with a variety of serious issues needing to be addressed urgently, such as increasing energy demands, environmental deterioration including global warming, and healthcare provision. Among these, the ever expanding healthcare needs are challenging and of particular importance, because maintaining good health conditions throughout the natural human life span is a fundamental requirement in most societies. It is inevitable, however, that with the passage of time, health status gradually deteriorates owing to aging. There has therefore been an increasing need to provide effective, convenient, and, in particular, noninvasive means to self-check major health conditions over a long period of time during normal daily life.

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The use of technologies with which to carry out long-term, regular, noninvasive monitoring of health conditions during normal daily life has been increasingly raised as a possible scheme for the early diagnosis and timely treatment of lifestyle-related diseases. In addition, it has been conjectured that this could help prevent, or at least control, such diseases and reduce healthcare costs. Furthermore, there are also needs to perform such health status monitoring of in- and outpatients having disorders requiring either acute life support or chronic therapies. Within this context, ubiquitous healthcare monitoring by noninvasive methods would be the most desirable.

The concept of this ubiquitous healthcare monitoring is basically to check health conditions anytime and anywhere and to manage individual physiological data obtained using, for example, a network system in a fully automated manner. In this sense, one of the most feasible methodologies would be ambulatory or wearable physiological monitoring, which means that biological sensors and/or miniaturized measuring units are to be carried by a subject or embedded into the user's clothes. Regarding this subject, brief descriptions of several recent developments by many investigators[1–6] and our group[7,8] are firstly presented in this paper.

Although such ambulatory monitoring would be relatively straightforward to implement in subjects while outside their dwelling or workplace, it is not always easy to achieve continuous monitoring smoothly after returning home. As the home is a place to relax and the time spent at home is relatively long each day, another possible methodology is required. In fact, health monitoring at home is one of the hot topics in the field of biomedical engineering, a major goal of which is to enable such monitoring everyday over a long period to evaluate health conditions, as mentioned above. One widely used approach is simply to have basic healthcare devices for home use, such as a thermometer, a sphygmomanometer, and a weighing scale, to be operated by individuals themselves. This approach is, however, difficult and bothersome for individuals to continue over long periods.

A new concept has recently been proposed for monitoring physiological variables in a fully automated manner without the need either to attach any sensors to the body or for individuals to carry out any operations, simply using home facilities such as a bed, a bathtub, and a rest room.[7,9–17] The techniques used in this approach do not disturb normal daily activities; thus, the monitoring is carried out in an unconstrained manner. Therefore, this concept would also be applicable and useful for patient monitoring in a hospital room. In this paper, outlines of such a monitoring system named "nonconscious physiological monitoring," which was developed by our group,[7,14–17] are also briefly introduced.

2. Ambulatory/Wearable Physiological Monitoring

Within the sphere of ambulatory monitoring, the Holter-type electrocardiogram (ECG) recorder, originally proposed by Holter,[18] and the portable sphygmomanometer called "ambulatory blood pressure monitor (ABPM)," which is based on the auscultation and/or cuff-oscillometric method,[19,20] are widely used in clinical medicine as key devices. Modern microelectronics and mechanical technologies have enabled us to produce more

compact and convenient devices for home use. Firstly, a few attempts at monitoring vital signs including ECG are briefly described.

2.1 *Recent attempts to monitor vital signs*

An interesting approach to monitoring ECG using textile electrodes has been reported by Rantanen *et al.*[1] Just recently, Biodevices S. A. in Portugal has commercialized a wearable ECG monitor based on this concept, as shown in Fig. 1. Developing both textiles and electronic miniaturization techniques has made it possible to incorporate electrodes into a T-shirt and much smaller electronic devices that can be worn and carried for long periods of time. As an application, the authors described the design of a survival clothing prototype for arctic environments, which could achieve ECG monitoring together with communication, including an emergency message, positioning, and navigation aids for the user.

The WEALTHY project, supported by the 5th Framework Information Science and Technology (IST) Programme of the European Union, is also noteworthy. Within this project, a new concept in healthcare was proposed, whereby the subject's vital signs were monitored through a groundbreaking woven sensor that could be worn without any discomfort for the user. This fabric sensor made of smart material in fiber and yarn form and integrated into a well-fitting cloth could be endowed with a wide range of electrophysical (such as conducting and piezoresistive) properties to obtain the simultaneous recording of vital signs. Figure 2 shows a prototype of the garment monitoring system,[2,3] which allows ECG and respiratory measurements. It is reported that such measurements provide reliable and satisfactory data as compared

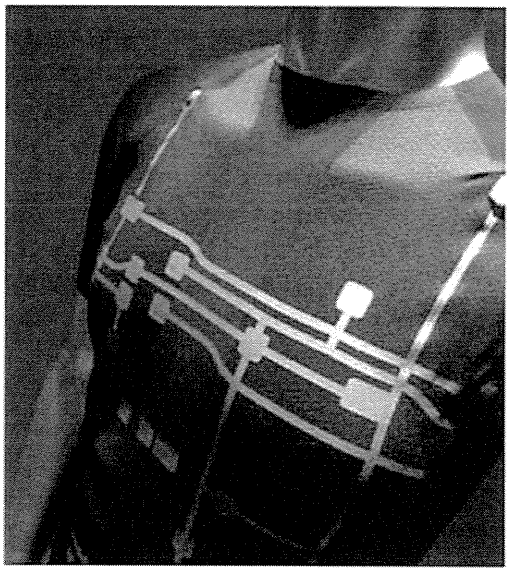

Fig. 1. Wearable ECG monitoring system with textile electrodes incorporated into a T-shirt,[1] recently commercialized by Biodevices S. A., in Portugal [http://inventorspot.com /articles /wearable_heart_monitor_vital_jackets_fashionable_vital_monitorin_24622].

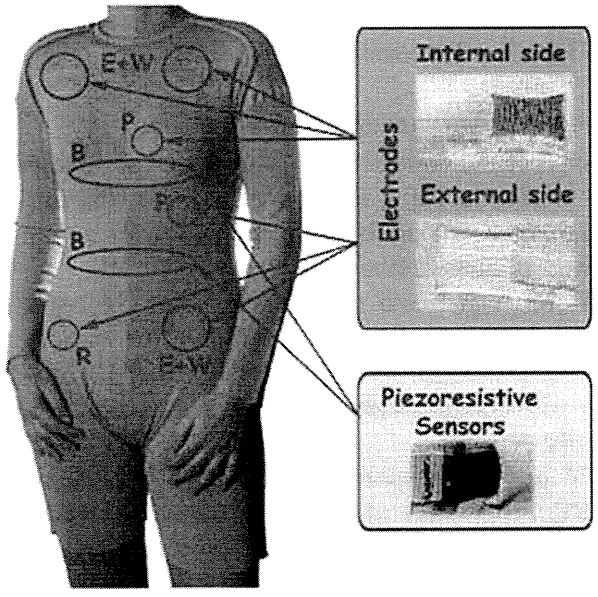

Fig. 2. Garment ECG and respiratory monitoring system with a woven sensor made of smart material in fiber and yarn form with conducting and piezoresistive properties (http://www.wealthy-ist.com/index.php?action=show_bversion). E+W, Einthoven-Wilson electrodes configuration; R, reference electrode; P, precordial leads; B, piezoresistive sensors for detecting breathing.

with a conventional standard method. The researchers of this project also state that the proposed system could assist patients during rehabilitation training or subjects working in extreme stressful environmental conditions, ensuring continuous surveillance.

In contrast to these monitoring concepts, miniaturized wireless sensor networks capable of autonomously controlled monitoring of vital signs and telecommunications for healthcare have recently been proposed.[4–6] A number of miniature wireless sensors placed on the body form a wireless body area network (W-BAN) that can monitor various vital signs, providing real-time feedback to the user and medical personnel. A conceptual diagram is shown in Fig. 3,[5] in which a subject carries an ECG measuring unit, a pulse oximeter (providing SpO_2), and trunk-angle and motion sensors along with a personal server to compose W-BAN using the ZigBee protocol.

2.2 *Ambulatory cardiovascular hemodynamic and activity monitoring*

Besides these innovative approaches described here, we have also continued developing ambulatory monitoring systems suitable for both clinical and home use, focusing particularly on the acquisition of data for the evaluation of cardiovascular hemodynamics and human activity. Following our earlier developments of ambulatory cardiovascular hemodynamic[20–24] and activity monitoring systems,[25–28] we have recently improved these two systems for more practical use.[7,8] Detailed operational performance, accuracy, and reliability of the two have already been successfully demonstrated and reported in the literature.[7,8,20–28] Brief descriptions of each system are therefore given below.

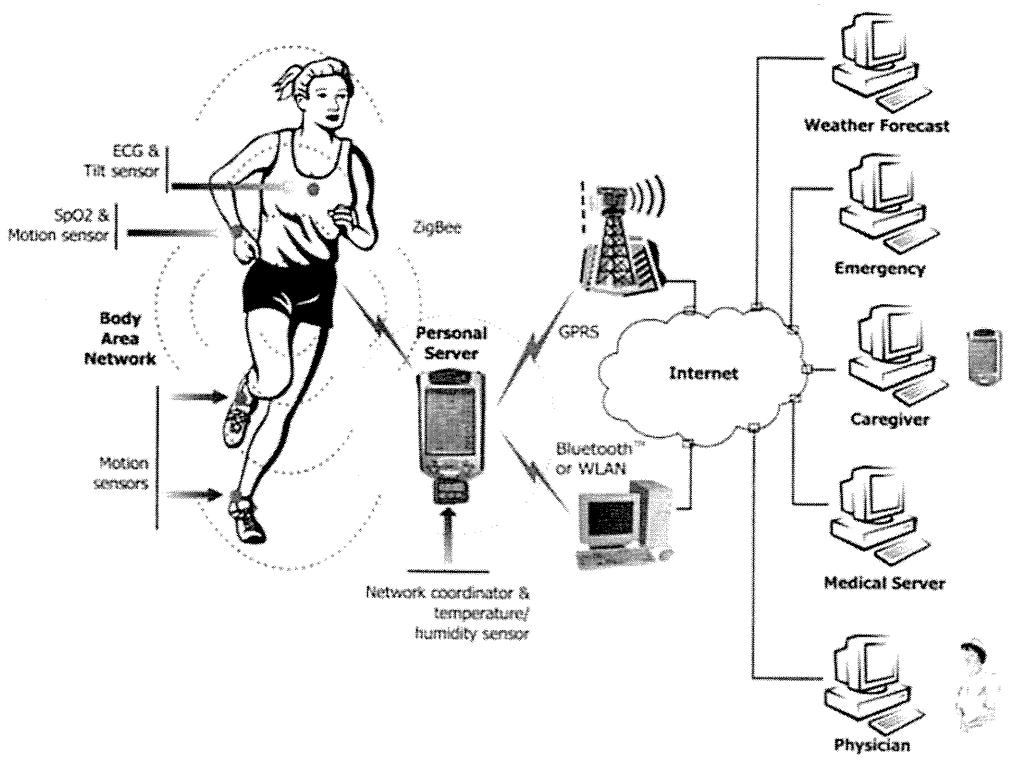

Fig. 3. Conceptual diagram showing wireless sensor network system. A user carries a number of tiny wireless vital sign sensors together with a personal server to create a wireless body area network (W-BAN) using the ZigBee protocol (from Fig. 1 in ref. 5).

2.2.1 *Beat-by-beat cardiovascular hemodynamic monitoring*

A conventional ABPM can measure blood pressure (BP) at a set interval of 30 min or more for convenient practical use and can thus acquire less than 48 data points per day owing to the limitations imposed by the measurement principle.[7,20] Because there are approximately 80,000–100,000 BP data per day produced by individual cardiac beats, only about 0.05% of the complete BP data set can be obtained by ABPM. It is logically desirable to acquire BP on a beat-by-beat basis. It is furthermore apparent that the acquisition of BP and cardiac output (CO) data together on a beat-by-beat basis combined with other cardiovascular data would be much more powerful in the detailed analysis of hemodynamic responses and autonomic regulation of the cardiovascular system in response to various daily activities.

With these as a background, we have recently developed a new beat-by-beat cardiovascular hemodynamic monitoring system both for ambulatory and stationary or medical use on the basis of a technological combination of the volume compensation[7,29] and transthoracic electrical admittance methods.[7,20,21,23,24,30,31] Figure 4 shows an overview of the monitoring situations for the system.

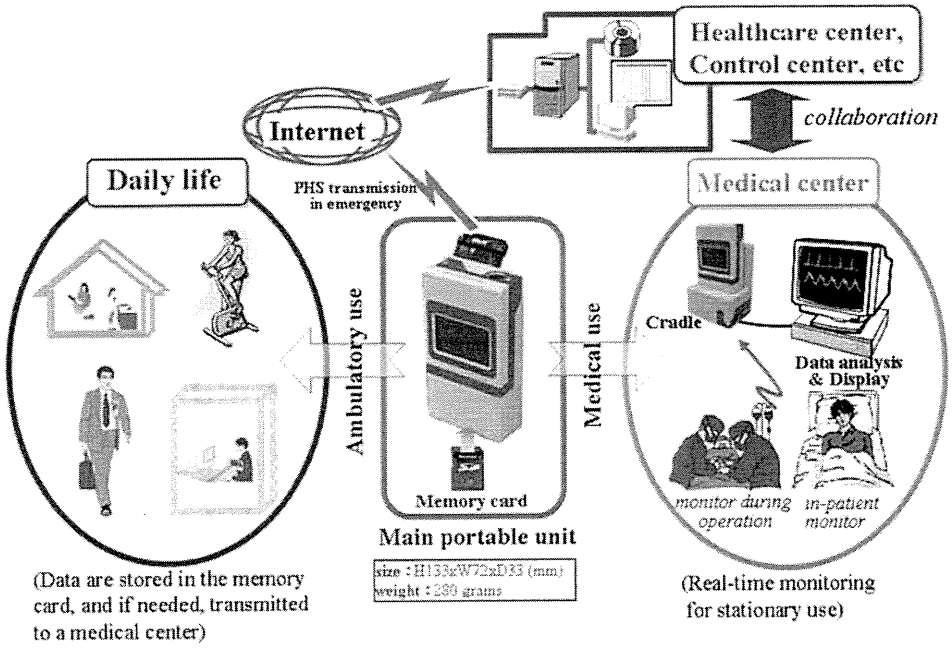

Fig. 4. Overview of beat-by-beat cardiovascular hemodynamic monitoring system both for ambulatory and stationary use. For further explanation, see text.

The essential parts of this system are (i) tetrapolar spot electrodes for CO measurement, (ii) a finger cuff unit with a photoplethysmographic sensor and a local pressurization cuff for the BP measurement, (iii) a cuff pressure controller, (iv) a main portable unit, (v) a cradle, and (vi) a conventional personal computer for data analysis and display. For ambulatory use, the subject carries the portable unit ($133\times72\times33$ mm^3; 280 grams including the battery) in a breast pocket together with the necessary sensors for the CO and BP measurements and the collected data are stored in a memory card. During operation, BP is compensated for the individual's heart level by measuring the hydrostatic pressure difference between the measuring site and the heart. For stationary or medical use, the portable unit housed in its cradle is connected to the computer for real-time monitoring of data as a time series during situations such as surgical operation and cases in intensive care unit (ICU) and coronary care unit (CCU) in a medical center.

The portable unit has eight functions: (1) BP measurement, (2) CO measurement, (3) signal processing and control of each measurement using a microprocessor unit, (4) data storage using a memory device, (5) data display using an LCD, (6) interactive communication between the unit and the cradle using a serial interface, (7) data transmission using a mobile phone system (PHS) for emergency situations, and (8) power supply using a lithium-ion rechargeable battery that is capable of continuous use for more than 6 h at present.

In the case of ambulatory use, the data stored in the portable unit are retrieved by the personal computer and an appropriate analysis is carried out to display the resultant

cardiovascular variables. The following 13 variables are processed on a beat-by-beat basis: systolic (SBP), mean (MBP) and diastolic BP (DBP), ECG R-R interval (RR), instantaneous heart rate (HR), stroke volume (SV), cardiac output (CO), pre-ejection period (PEP) as an index of sympathetic activity, ventricular ejection time (Ts), pulse transit time (PTT), peripheral vascular resistance (TPR), rate pressure product (RPP) as an index of cardiac oxygen consumption, and respiration rate (Resp). Using the derived data, the computer can then show the 13 processed variables on the display.

Figure 5 is an example of a 6-hour trend chart, showing 7 of 13 hemodynamic parameters, RR, BP (SBP/MBP/DBP), SV, CO and TPR, obtained in a healthy male subject (22 yrs) during a part of his normal daily activities (from 10:00 to 16:00 h). He was instructed to move freely and perform various normal activities, such as walking, desk work, exercise, and postural changes from sitting to standing for example, as indicated in the uppermost part of this figure. It is clearly observed that the increases in BP and CO during bicycle riding, as well as the fluctuations in each of the parameters produced by postural changes such as sit-to-stand motion, sit-to-lie motion, and so on, demonstrate the dynamic changes in chosen parameters in response to various activities.

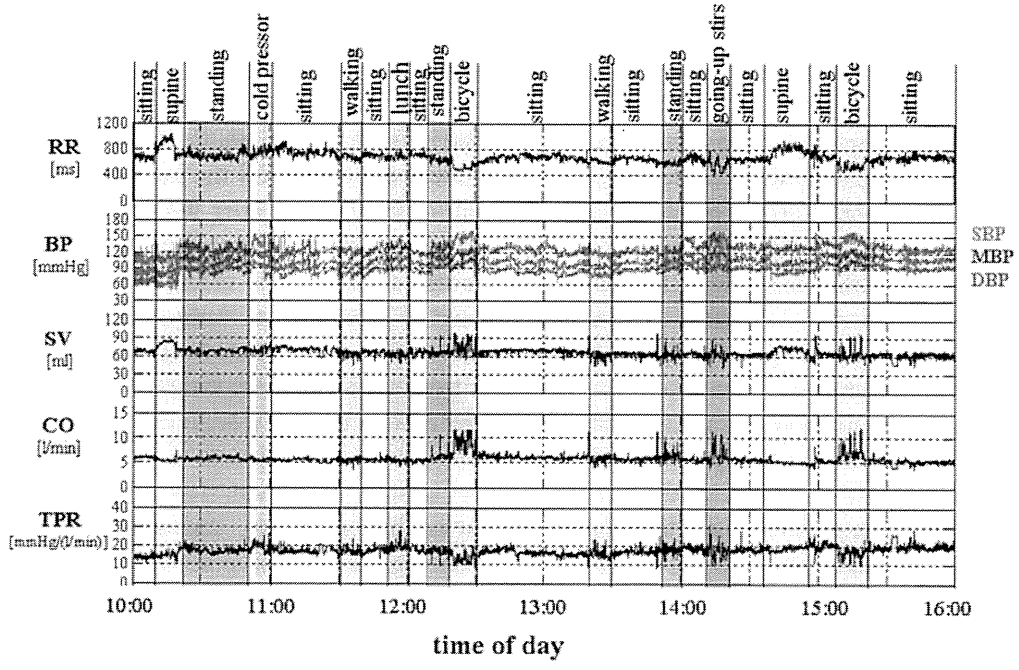

Fig. 5. Example of 6-hour trend chart, showing hemodynamic parameters ECG R-R interval (RR), blood pressure (BP; systolic (SBP), mean (MBP) and diastolic BP (DBP)), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) obtained in a healthy male subject (22 yrs) during a certain time of the day (from 10:00 to 16:00). Various activities are indicated in the uppermost part of this figure.