In the bed, a flat sensor (800×15×8 mm³) is fixed under a pillow or a bed mat. It comprises four vinyl tubes filled with silicone oil sandwiched by two acrylic plates,[17] the width of which is aligned along a bed side. One end of each tube is connected to a pressure sensor and the other end is closed. The inner pressure in each tube changes in accordance with respiration, cardiac beating, and snoring, and each component can be detected using an appropriate digital filter. Moreover, periods of apnea and hypopnea can be detected from the decrease in amplitude of the respiration signal for more than 10 s, which is based on the definition of sleep apnea syndrome (SAS), using a fully automated analytical program. The DC level of the pressure output can provide information on whether the subject is lying on the bed.

For ECG monitoring in the bath, four stainless steel electrodes are fixed to the inner wall of the bathtub essentially surrounding the subject's chest, so as to place them in the standard Einthoven's triangle configuration. One of the four electrodes is used as the reference electrode placed far from the other three electrodes. The potential differences between two electrodes, similar to the conventional lead-I, lead-II, and lead-III, are amplified to obtain a raw ECG signal. This signal contains a baseline fluctuation due to respiration, and thus, can be filtered with a digital filter, obtaining a clear ECG and a respiration component.[12] The fluctuations of R-R intervals in accordance with respiratory sinus arrhythmia are also used for the detection of the respiratory component.[17]

Figure 10 shows examples of recordings of the changes in body weight during urination (a) and those in BP measurement (b) using the toilet-installed monitoring system in a healthy male subject (25 yrs). Usually, after standing on the platform or sitting on the toilet seat, very large artifact signals due to body movements are observed immediately before and after urination (or defecation). These components are reduced due to less motion during urination (or defecation); therefore, the system can detect the body weights at the start and end of excretion, and thus, excretion weight can be obtained from the difference between the two body weights. Furthermore, the other components, i.e., ballistocardiogram (BCG) in association with cardiac beats, are observed superimposed on the weight change signal, as shown in Fig. 10(a). The rate of urination is obtained from the weight change signal smoothed by an appropriate filter, obtaining urination flow rate.

It is also noted that the initial phase of a BCG signal originates from the ejecting blood flow from the ventricle,[40,41] i.e., differentiation of the ventricular volume change. Therefore, stroke volume (SV) and thus cardiac output (CO = SVx (heart rate)) could be estimated from BCG signals together with BP as obtained below.[41]

In Fig. 10(b), the simultaneously obtained records of the pulsatile component of the photoplethysmogram (PGac) are shown with the applied contact pressure for BP measurement. The pressure measurement reference is compensated for the subject's heart level by the hydrostatic pressure difference between the measuring site and the heart. According to the volume-oscillometric method,[39] the systolic (SBP) and the mean BP (MBP) can be indirectly determined from the applied pressure corresponding respectively to the systolic end point and the maximum amplitude point of PGac.

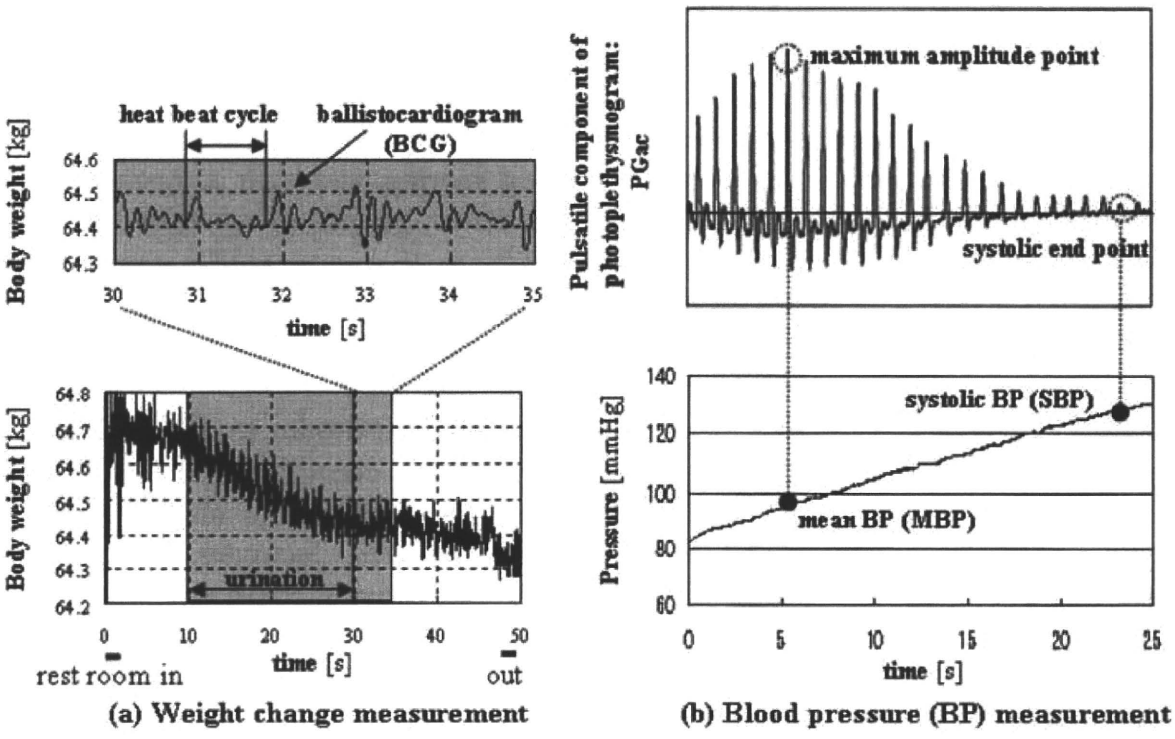


Fig. 10 Example of recordings using the toilet-installed monitoring system obtained from a healthy male subject (25 yrs). In (a), the signals for body weight (BW) change following urination and the ballistocardiogram (BCG) superimposed on the BW signals (upper part) are shown. (b) shows the simultaneous records of the pulsatile component of the photoplethysmogram (PGac) and the applied contact pressure for the measurement of blood pressure (BP). By the volume-oscillometric method, systolic (SBP) and mean BP (MBP) can be indirectly determined from applied pressure corresponding respectively to the systolic end point and the maximum amplitude point of PGac.

The upper two records in Fig. 11 show an example of respiration signals obtained by the bathtub electrodes (upper panel) and a chest band (lower panel) before and immediately after simulated drowning with the head bent forward in a healthy male subject (24 yrs). In the lower two records are shown ECG signals obtained by the bathtub electrodes (upper panel) and ECG electrodes directly attached to the subject's body surface (lower panel) during a part of drowning indicated by a shadow in the upper records. It is clearly observed that the respiration and ECG signals detected by the two methods agree well with each other, and that the ECG signals continue to be observed but no respiration signals can be obtained during the simulated drowning.

In the upper two records of Fig. 12 are shown respiration signals using the under-pillow sensor (upper panel) and a respiration chest band (lower panel) before and immediately after a period of simulated apnea obtained in a healthy male subject (25 yrs) in the supine position. The lower two records, which are the shadow part in the upper records of Fig. 12, show the cardiac pulse signal obtained by the under-pillow sensor (upper panel) and the ECG signal detected from the ECG electrodes directly attached to the body surface (lower panel). From these results, it is demonstrated that the respiration

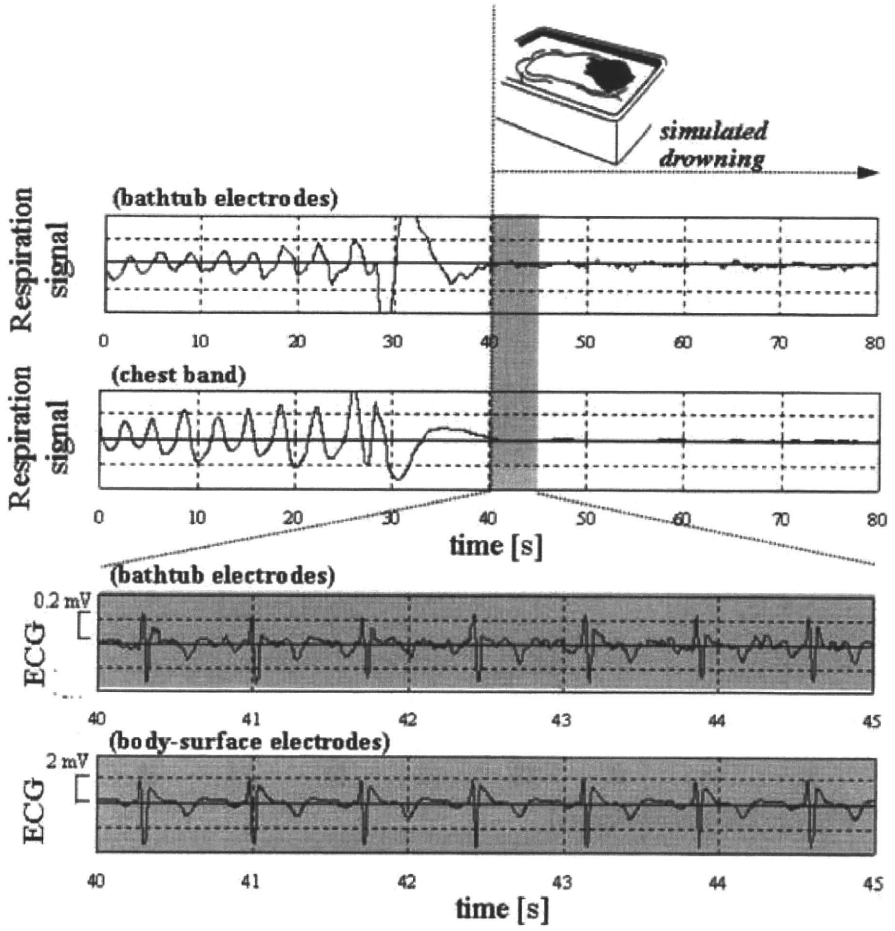


Fig. 11. Example of respiration signals (upper part) obtained by the bathtub electrodes (upper record) and a chest band (lower record) before and immediately after simulated drowning with the head bent forward in a healthy male subject (24 yrs). In the lower two records are shown ECG signals obtained by the bathtub electrodes (upper panel) and ECG electrodes directly attached to the subject's body surface (lower panel) during a part of drowning indicated by a shadow in the upper records.

and cardiac pulse signals obtained from the under-pillow sensor coincide well with those obtained from the body attachment sensors, and the period of apnea could also be definitely observed in respiration signals.

To investigate the applicability of this mode of health status monitoring in subjects with established clinical conditions, we have further developed the system to produce a new fully automated monitoring system, combining all the monitoring devices, and installed this in hospital rooms in Imizu City Hospital and Fujimoto Hayasuzu Hospital.[42] To date, we have found that the system is suitable for checking the health status of patients with chronic diseases, such as cardiac infarction and SAS, and that this monitoring appears superior to the conventional approach in the sense that it places less strain on the patient because there is no attachment of biological sensors. Further important data including the validity as well as clinical usefulness of the system have been reported.[42,43]

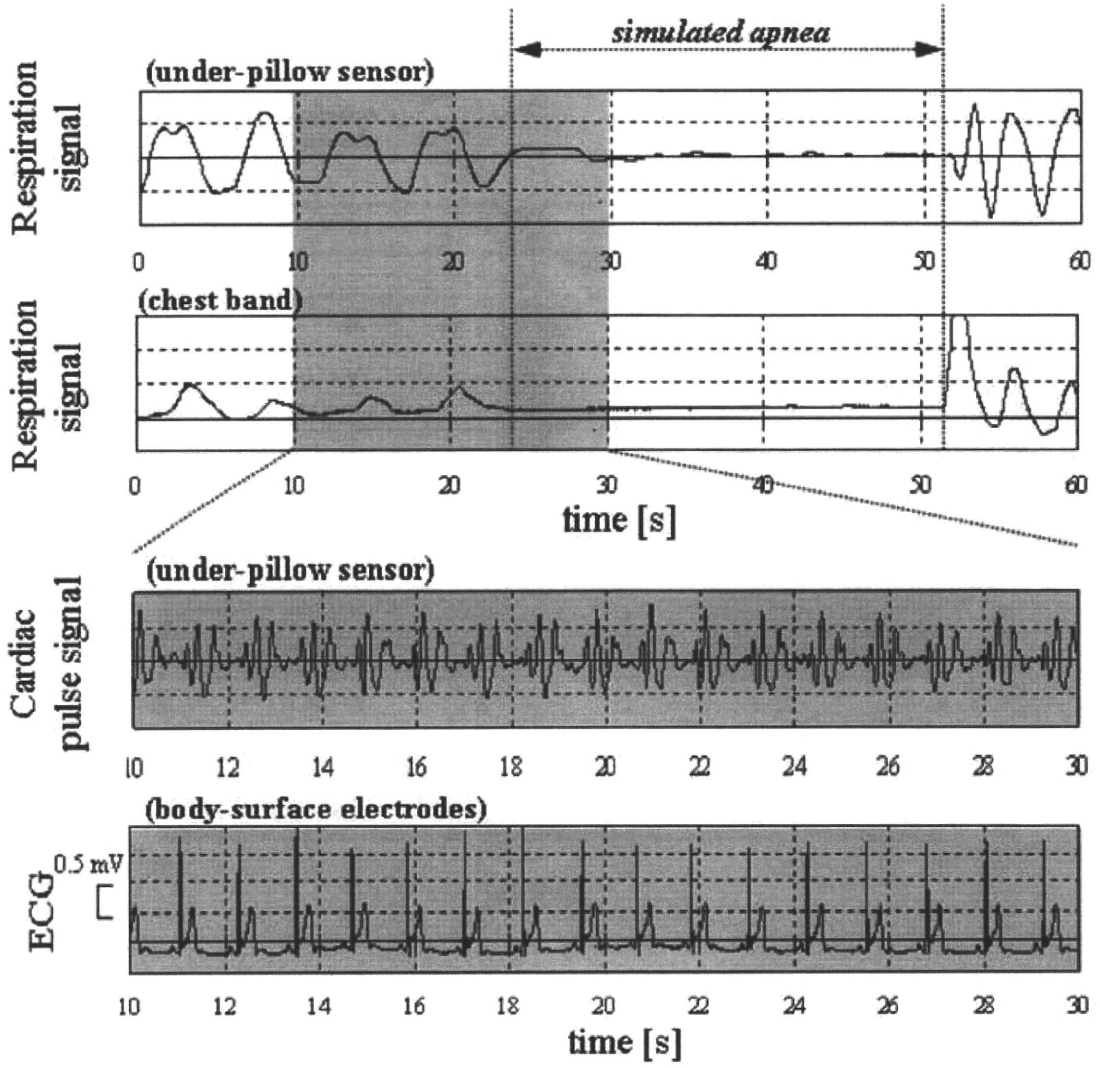


Fig. 12. Example of respiration signals (upper part) obtained by the under-pillow sensor (upper record) and a respiration chest band (lower record) before and immediately after a period of simulated apnea in a healthy male subject (25 yrs) in the supine position. In the lower part of this figure are shown cardiac pulse signal obtained by the under-pillow sensor (upper record) and ECG signal detected from the body surface electrodes (lower record) during a certain time indicated by a shadow in the upper part.

## 4. Summary and Future Developments

Recent developments and the present status of noninvasive bioinstrumentation for healthcare were briefly introduced in this review, including in particular the developments we have achieved. There are at present two research approaches in terms of monitoring techniques; one is ambulatory or wearable physiological monitoring and the other is nonconscious physiological monitoring. In light of the growth of the aging society, which has created what might be regarded as a longevity crisis, healthcare is one of the most serious and worldwide issues to address. Simple, convenient, and truly

ubiquitous healthcare monitoring in a fully automated as well as in a noninvasive manner could be the most useful and desirable.

The two research approaches described in this paper appear innovative and groundbreaking, particularly in the developments of instrumented garment systems and W-BAN with miniaturized sensors. It is optimistically anticipated that such easy-to-use devices could be made available at reasonable costs in the future, although there are still a number of challenging obstacles to be overcome, such as the rather conflicting requirements for size, wear comfort, operating procedures, precision, power management, and reliability.[1–6] Another problem is the fact that at present such devices only provide a limited range of physiological information derived from ECG, respiration, and simple motion signals. Given this situation, the ambulatory cardiovascular and activity monitoring devices described here would be even more suitable for practical use through further miniaturization, making them smaller and lighter with easier and more comfortable attachment to the body.

The approach described here for achieving nonconscious physiological monitoring at home would appear at the present time to be a near ideal solution, with good potential for practical use. The justification for this view is as follows. The individuals who might benefit from regular health assessment generally find using commercially available medical devices such as a BP monitor and a weighing scale quite troublesome or find it difficult to monitor their health conditions daily over a long period because these devices need the attachment of a biological sensor and manual operation for measurements. This inconvenience obstructs and deters long-term daily monitoring. In the nonconscious monitoring approach, however, the location of the systems in the toilet space, bathtub, and bed is considered to be very convenient and appropriate, because a subject at home uses these places everyday and reliable measurements can therefore be made within this stable and predictable situation.

It is therefore a fact that the nonconscious monitoring approach has made technological breakthroughs in achieving easier and more convenient acquisition of various physiological parameters at home. There are, however, still important practical issues to be solved in terms of interpretation methodology of a huge number of data and protection of personal information.

Taking a comparison of these ambulatory and nonconscious monitoring approaches into consideration, it is noted that, by addressing various issues mentioned above to complement both techniques, each approach will be practically available in a parallel way and the combination of these two will provide a much more useful and promising means.

In the so-called 'super-aging society,' these techniques could be relevant, contributing in many fields such as personal healthcare, medical care, and rehabilitation. To promote ubiquitous healthcare monitoring further, the establishment of appropriate social infrastructure that meets the needs of healthcare is urgently needed. Efforts to produce much more human-friendly sensing systems, where a number of practical problems still remain, are likely to be resolved through the considerable recent dramatic advances in microelectronic, micromechanical, information, and communication technologies.

## Acknowledgements

The author wishes to thank Dr. Peter Rolfe, Director of Biohorizon Ltd. and Professor of Harbin Institute of Technology, for kind help in preparing the manuscript, Dr. Mitsuhiro Ogawa and Dr. Kosuke Motoi, Kanazawa University, for helpful discussion and assistance in the survey of current publications, Professor Shinobu Tanaka, Dr. Takehiro Yamakoshi, Kanazawa University, Dr. Hidetsugu Asanoi, Director of Imizu City Hospital, Dr. Toshiro Fujimoto, Administrative Director of Yokakai Association and Fujimoto Hayasuzu Hospital, Dr. Yuji Higashi and Mr. Tadahiko Yuji, Rehabilitation Center of Fujimoto Hayasuzu Hospital, for valuable discussion and considerable assistance during the progress of the research programs on instrumentation, data analysis, experimentation, and clinical evaluation. The studies were partly supported by the Knowledge-based Cluster Creation Project (Ishikawa High-tech Sensing Cluster, 2004–2009), and Grants-in-Aid for Scientific Research (No. 14208105, 2002–2004; No. 17300149, 2005–2007; No. 19700469, 2007–2008) from the Japan Ministry of Education, Culture, Sports, Science and Technology, and Strategic Information and Communications R&D Promotion Programme (SCOPE; No. 102305004, 2010) from the Japan Ministry of Internal Affairs and Communications, for which I wish to express my sincere appreciation.

## References

1 J. Rantanen, J. Impiö, T. Karinsalo, M. Malmivaara, A. Reho, M. Tasanen and J. Vanhala: Personal and Ubiquitous Computing **6** (2002) 3.
2 L. Bourdon, S. Coli, G. Loriga, N. Taccini, B. Gros, A. Gemignani, D. Cianflone, F. Chapotot, A. Dittmar and R. Paradiso: Computers in Cardiology **32** (2005) 615.
3 R. Paradiso, G. Loriga, N. Taccini, A. Gemignani and B. Ghelarducci: J. Telecommun. Inf. Technol. **2** (2005) 105.
4 E. Jovanov, A. O. Lords, D. Raskovic, P. Cox, R. Adhami and F. Andrasik: IEEE Eng. Med. Biol. Magazine, May/June (2003) 49.
5 E. Jovanov, A. Milenkovic, C. Otto and P. C. Groen: J. NeuroEng. Rehabilitation **2** (2005) (http.//www.jneuroengrehab.com/content/2/1/6: Accessed on April 2010).
6 C. Otto, A. Milenkovic, C. Sanders and E. Jovanov: J. Mobile Multimedia **1** (2006) 307.
7 K. Yamakoshi: Non-Invasive Cardiovascular Hemodynamic Measurements, Sensors in Medicine and Health Care, eds. P. A. Öberg, T. Togawa, F. A. Spelman (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2004) p. 107.
8 K. Motoi, S. Tanaka, Y. Kuwae, T. Yuji, Y. Higashi, T. Fujimoto and K. Yamakoshi: J. Robotics and Mechtronics **19** (2007) 656.
9 M. Ishijima and T. Togawa: Clin. Phys. Physiol. Meas. **10** (1989) 171.
10 M. Ishijima: Med. Biol. Eng. Comput. **35** (1997) 685.
11 Y. G. Lim, K. K. Kim and K. S. Park: IEEE Trans. Biomed. Eng. **54** (2007) 718.
12 P. Chow, G. Nagendra, J. Abisheganaden and Y. T. Wang: Physiol. Meas. **21** (2000) 345.
13 K. Watanabe, T. Watanabe, H. Watanabe, H. Ando, T. Ishikawa and K. Kobayashi: IEEE Trans. Biomed. Eng. **52** (2006) 2100.
14 K. Yamakoshi: Frontiers Med. Biol. Eng. **10** (2000) 139.
15 S. Tanaka, M. Nogawa and K. Yamakoshi: Proc. IEEE Eng. Med. Biol. 27th Annual Conf. Shanghai, CD-ROM (2005).

16 X. Zhu, W. Chen, T. Nemoto, Y. Kanemitsu, K. Kitamura, K. Yamakoshi and D. Wei: IEEE Trans. Biomed. Eng. **53** (2006) 2553.
17 K. Motoi, S. Kubota, A. Ikarashi, M. Nogawa, S. Tanaka, T. Nemoto and K. Yamakoshi: Proc. 29th Annual Conf. IEEE Engineering in Medicine and Biology Society (2007) 1826.
18 N. J. Holter: Science **134** (1961) 1214.
19 G. W. Mauck, C. R. Smith, L. A. Geddes and J. D. Bourland: J. Biomech. Eng. **102** (1980) 28.
20 K. Yamakoshi: J. Ambul. Monit. **4** (1991) 123.
21 K. Yamakoshi, A. Kawarada, A. Kamiya, H. Shimazu and H. Ito: Med. Biol. Eng. Comput. **23** (1985) 459.
22 S. Tanaka and K. Yamakoshi: Med. Biol. Eng. Comput. **34** (1996) 441.
23 K. Yamakoshi, M. Nakagawara and S. Tanaka: Biocybern. Biomed. Eng. **17** (1997) 181.
24 M. Nakagawara and K. Yamakoshi: Med. Biol. Eng. Comput. **38** (2000) 17.
25 K. Motoi, S. Tanaka, M. Nogawa and K. Yamakoshi: SICE Annual Conf. Proc. (2003) 563.
26 S. Tanaka, K. Yamakoshi and P. Rolfe: Med. Biol. Eng. Comput. **32** (1994) 357.
27 K. Motoi, Y. Higashi, Y. Kuwae, T. Yuji, S. Tanaka and Y. Yamakoshi: Proc. 27th Annual Conf. IEEE Eng. Med. Biol. CD-ROM (2005).
28 K. Motoi, K. Ikeda, Y. Kuwae, T. Yuji, Y. Higashi, M. Nogawa, S. Tanaka and Y. Yamakoshi: Proc. 28th Annual Conf. IEEE Eng. Med. Biol. Soc. CD-ROM (2006).
29 K. Yamakoshi, H. Shimazu and T. Togawa: IEEE Trans. Biomed. Eng. BME-**27** (1980) 150.
30 H. Ito, K. Yamakoshi and T. Togawa: J. Appl. Physiol. **40** (1976) 451.
31 A. Ikarashi, M. Nogawa, S. Tanaka and K. Yamakoshi: Proc. 29th Annual Conf. IEEE Eng. Med. Biol. Soc. (2007) 4580.
32 A. Hendry, W. Gilchrist, G. Duncan, A. L. Evans and D. C. Smith: Med. Biol. Eng. Comput. **28** (1990) 602.
33 S. Miyazaki: IEEE Trans. Biomed. Eng. **44** (1997) 753.
34 R. Williamson and B. J. Andrews: Med. Biol. Eng. Comput. **39** (2001) 1.
35 R. E. Mayagoitia, J. C. Lotters, P. H. Veltink and H. Hermens: Gait and Posture **16** (2002) 55.
36 M. Sekine, T. Tamura, M. Akay, T. Fujimoto, T. Togawa and Y. Fukui: IEEE Trans. Rehab. Eng. **10** (2002), 188.
37 B. Najafi, K. Aminian, A. Paraschiv-Ionescu, F. Loew, C. J. Bula and P. Robert: IEEE Trans. Biomed. Eng. **50** (2003) 711.
38 H. Dejnabadi, B. M. Jolles, E. Casanova, P. Fua and K. Aminian: IEEE Trans. Biomed. Eng. **53** (2006) 1385.
39 K. Yamakoshi, H. Shimazu, M. Shibata and A. Kamiya: Med. Biol. Eng. Comput. **20** (1982) 307 and 314.
40 K. Yamakoshi: Proc. 18th Annual Intern. Conf. IEEE Eng. Med. Biol. Soc. (1996) 10.
41 K. Yamakoshi: IEEE Rev. Biomed. Eng. **2** (2009) 2.
42 K. Motoi, M. Ogawa, H. Ueno, Y. Kuwae, A. Ikarashi, T. Yuji, Y. Higashi, S. Tanaka, T. Fujimoto, H. Asanoi and K. Yamakoshi: Proc. 31st Annual Intern. Conf. IEEE Eng. Med. Biol. Soc. (2009) 4323.
43 K. Motoi, A. Ikarashi, S. Tanaka, K. Yamakoshi. Ubiquitous Healthcare Monitoring for Daily Life, Distributed Diagnosis and Home Healthcare, eds. U. R. Acharya *et al.* (American Scientific Publishers, 2010) (in press).

## About the Author

***Ken-ichi Yamakoshi***

Final affiliated college and degrees: He received his B. Sc and M.Sc degrees from Waseda University in 1970 and 1972, and D. Med. and D. Eng. degrees from Tokyo Medical and Dental University in 1979 and Waseda University, Tokyo, Japan in 1982, respectively.

Career summary: Professor Yamakoshi is a biomedical engineer with a career spanning about 40 years. He started as a Research Assistant at Tokyo Women's Medical College from 1972 to 1973, then as a Research Assistant at Tokyo Medical and Dental University from 1974 to 1980, an Associate Professor at Hokkaido University from 1980 to 1994, and has been a Professor at Kanazawa University since 1994. He is also currently a Visiting Professor at Dalian University, Dalian, China, Heilongjiang University, Harbin, China, and at Waseda University. Much of his research over this period has been concerned with noninvasive and/or ambulatory physiological measurement and instrumentation, nonconscious healthcare monitoring, human support systems, artificial organs, cardiovascular biomechanics and rehabilitation engineering. He has been an Associate Editor of the Institute of Electrical and Electronics Engineers (IEEE) Transactions on Biomedical Engineering and IEEE Transactions on Information Technology in BioMedicine, and an Area Editor of IEEE Reviews in Biomedical Engineering. He has also been the Director of two venture companies set up through research achievements.

Special field of study: Physiological measurement and instrumentation, healthcare science, cardiovascular and orthopedic biomechanics, rehabilitation engineering.

Society memberships: International Federation of Medical and Biological Engineering, IEEE Engineering in Medicine and Biology Society, Japanese Society for Medical and Biological Engineering, Japan Society of Mechanical Engineers, Society of Instrument and Control Engineers, Japan Association for Clinical Monitoring, and so on.

循環器内科，68(5)：496-498，2010

話　題

# アルツハイマー病に用いられるドネペジルの抗心不全作用*

佐　藤　隆　幸**

**Key Words** : acetylcholine, heart failure, remodeling, vagus nerve, ventricular function

## はじめに

われわれはこれまでに，迷走神経の電気刺激によって慢性心不全の進行が防止され，生命予後が改善される可能性を動物実験で明らかにしてきた[1]．近年では，イスラエルのBioControl Medical社によって植え込み型迷走神経刺激装置が開発され，臨床試験が行われている．研究の成功が大いに期待されるところである．

一方われわれは，迷走神経刺激が抗心不全作用を発揮する機序について分析するとともに[2)~4)]，既存の臨床薬剤の中で同様の機序を駆動する可能性のあるものを探索してきた．

塩酸ドネペジル(アリセプト®)はアルツハイマー病における認知症の進行を抑制する薬剤としてわが国で開発され，脳内のアセチルコリンエステラーゼ(AChE)を抑制することによって，その効果を発揮すると考えられている．われわれは最近，マウス心不全モデルを用いた研究によって，ドネペジルが抗心不全作用を有することを明らかにした[5]．

## マウスの慢性心不全モデル

体重35g前後の雄マウスに腹部大動脈―下大静脈シャント術を行い，容量負荷型心不全モデルを作成した．心不全モデルの妥当性を術後4週で検討した．表1に示すように，4週目には心室拡張を伴った心不全が進行していると考えられた．覚醒下心拍数は偽手術群に比べ，むしろ減少していた．おそらく，著名な心房拡張と線維化によってもたらされたと考えられる．ランゲンドルフ灌流標本による圧容積関係の解析では$V_0$の増加と$E_{es}$の低下が認められ，シャント術後4週目には心臓ポンプ機能の低下がもたらされていると考えられた．

## ドネペジルの不全心に与える影響

腹部大動脈―下大静脈シャント術から4週後にマウスを無作為に2群に分け，無治療群とドネペジル治療群とした．治療群では飲水中にドネペジルを溶かし，1日用量がkg体重あたり5 mgになるようにした．用量設定は，ドネペジルを用いたマウスやラットの神経学的研究のプロトコールを参考に行った．4週間の治療後に血行動態を評価した．

表2に示すように，無治療群では心室拡張と心機能低下がさらに進展し，心臓リモデリングが進行している．一方ドネペジル治療群では，このような心不全増悪が有意に防止されている．心不全重症度の臨床マーカーのひとつである脳型ナトリウム利尿ペプチドの心室での発現も治療群では低下し，心不全の改善を示唆していると考えられる．

## ドネペジルの慢性心不全の生命予後に与える影響

腹部大動脈―下大静脈シャント術から4週後にマウスを無作為に2群に分け，無治療群とド

* Anti-Alzheimer's drug, donepezil, improves survival after chronic heart failure in mice.

** Takayuki SATO, M.D., Ph.D.: 高知大学医学部循環制御学〔〒783-8505 南国市岡豊町小蓮〕; Department of Cardiovascular Control, Kochi Medical School, Nankoku 783-8505, JAPAN

表1　心不全モデルの特徴

| | | 偽手術群 | シャント術群 |
|---|---|---|---|
| 覚醒下での計測 | ・匹数 | 12 | 12 |
| | ・心拍数(beats/min) | 700±13 | 643±9* |
| | ・収縮期血圧(mmHg) | 112±7 | 103±3 |
| 麻酔下での計測 | ・匹数 | 5 | 5 |
| | ・心拍数(beats/min) | 480±53 | 470±24 |
| | ・左室拡張末期圧(mmHg) | 3.71±0.33 | 8.05±1.02* |
| | ・左室収縮ピーク圧(mmHg) | 135.6±25.7 | 119.6±10.1* |
| | ・$dp/dt_{max}$(mmHg/sec) | 8,120±1,134 | 5,620±881* |
| 灌流標本での計測 | ・匹数 | 7 | 7 |
| | ・$V_0$(μl) | 1.2±0.2 | 2.2±0.3* |
| | ・$E_{es}$(mmHg/μl) | 1.96±0.16 | 1.32±0.04* |
| 心重量の計測 | ・匹数 | 12 | 12 |
| | ・両心室重量(mg/g) | 4.48±0.18 | 5.56±0.10* |

$dp/dt_{max}$：左室圧の時間微分ピーク値，$V_0$：収縮期末圧容積関係における容積軸切片，$E_{es}$：収縮期末エラスタンス．値は平均±標準偏差．* $P<0.05$

表2　ドネペジル治療の不全心に与える影響

| | | 無治療群 | 治療群 |
|---|---|---|---|
| 覚醒下での計測 | ・匹数 | 20 | 20 |
| | ・心拍数(beats/min) | 573±11 | 643±11* |
| | ・収縮期血圧(mmHg) | 105±10 | 108±15 |
| 麻酔下での計測 | ・匹数 | 10 | 10 |
| | ・心拍数(beats/min) | 522±51 | 519±42 |
| | ・左室拡張末期圧(mmHg) | 14.9±0.8 | 10.2±1.6* |
| | ・左室収縮ピーク圧(mmHg) | 91.6±11.3 | 104.3±8.6* |
| | ・$dp/dt_{max}$(mmHg/sec) | 4,506±997 | 5,961±562* |
| 灌流標本での計測 | ・匹数 | 10 | 10 |
| | ・$V_0$(μl) | 5.1±0.4 | 3.1±0.3* |
| | ・$E_{es}$(mmHg/μl) | 0.96±0.09 | 1.47±0.05* |
| 心重量の計測 | ・匹数 | 20 | 20 |
| | ・両心室重量(mg/g) | 6.07±0.78 | 5.64±0.68* |
| 左室でのBNP発現 | ・匹数 | 10 | 10 |
| | ・BNP mRNA(a.u.) | 0.56±0.08 | 0.37±0.06* |

$dp/dt_{max}$：左室圧の時間微分ピーク値，$V_0$：収縮期末圧容積関係における容積軸切片，$E_{es}$：収縮期末エラスタンス，BNP：脳型ナトリウム利尿ペプチド，a.u.：任意単位．値は平均±標準偏差．* $P<0.05$

ネペジル治療群とし，50日間の生存率を観察した．

図1にKaplan-Meier生存率曲線を示す．無治療群では50日の観察期間中に約半数が死亡したが，治療群では2割の死亡数であった．ドネペジルによって相対的死亡危険率がおおよそ6割減少した．

## ドネペジルの抗心不全作用のメカニズム

ドネペジルの抗心不全作用として，当初β遮断薬のような徐脈作用を介する機序が想定されたが，表2に示すように，このような機序は否定的であった．そこで，新生仔心筋細胞培養系を用いてドネペジルの効果を検証した．その結果，ドネペジルは心筋細胞に作用して，hypoxia inducible factor-1α(HIF-1α)，vascular endothelial growth factor(VEGF)の発現を刺激すること，その作用がムスカリン受容体遮断薬，ニコチン受容体遮断薬では阻害されないことを見出した．

詳しい機序は不明であるが，ドネペジルが直接心筋細胞に作用してHIF-1αやVEGFなどの細胞生存因子の合成を刺激し，心筋細胞死を抑制す

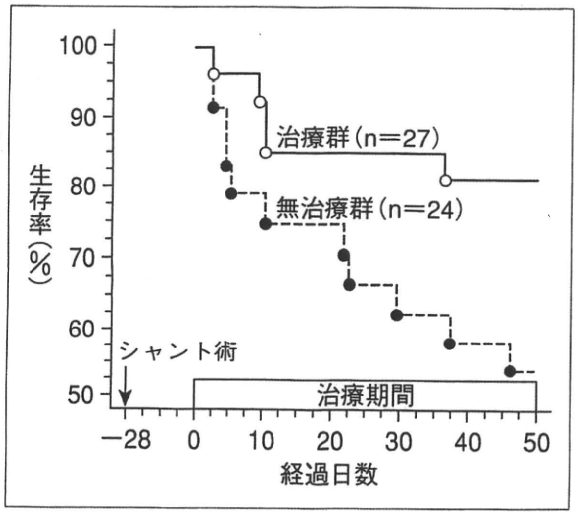


図1　ドネペジルの生存率に与える影響

ることによって抗心不全効果をもたらした可能性がある．これらの効果は，AChE阻害作用とは独立したものである可能性が高く，たいへん興味深い．

## ドネペジルの心血管死に与える影響に関する臨床研究

これまでの動物実験の結果をふまえて，共同研究機関である米国Vanderbilt大学のSatoらがドネペジルの心血管死に与える影響について後ろ向き調査を行った[6]．アルツハイマー型認知症例でドネペジルを服用している例と服用していない例を中心に平均30か月の観察を行ったところ，服用群では心血管死のリスクが4割程度減少していることが明らかになった．多変量解析の結果でも，ドネペジル服用が独立したリスク要因であることが示された．しかし，比較した症例数がそれぞれ80例程度と少数であること，後ろ向き調査であることから，より信頼性の高い結果を得るために，より大規模な前向き調査が期待される．

## おわりに

アルツハイマー病の認知障害の進行を防止する薬剤として幅広く使用されているドネペジルが，抗心不全効果や心血管死防止効果を発揮する可能性を示唆する知見が得られつつある．ごく最近では，ドネペジルが心筋細胞や血管内皮細胞に作用してアセチルコリン(ACh)の産生・放出を刺激し[7]，さらに，*de novo* AChのautocrine, paracrine的機序により，心筋細胞死を防止したり，血管新生を誘導する可能性も示唆されている[8]．今後，さらに研究が進めば，ドネペジルが慢性心不全や虚血性心疾患に対する治療薬の新機軸になる可能性がある．

## 文　献


1) Li M, Zheng C, Sato T, et al. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation 2004 ; 109 : 120.

2) Ando M, Katare RG, Kakinuma Y, et al. Efferent vagal nerve stimulation protects heart against ischemia-induced arrhythmias by preserving connexin43 protein. Circulation 2005 ; 112 : 164.

3) Kakinuma Y, Ando M, Kuwabara M, et al. Acetylcholine from vagal stimulation protects cardiomyocytes against ischemia and hypoxia involving additive non-hypoxic induction of HIF-1 alpha. FEBS Lett 2005 ; 579 : 2111.

4) Katare RG, Ando M, Kakinuma Y, et al. Vagal stimulation prevents reperfusion injury through inhibition of opening of mitochondrial permeability transition pore independent of the bradycardiac effect. J Thorac Cardiovasc Surg 2009 ; 137 : 223.

5) Handa T, Katare RG, Kakinuma Y, et al. Anti-Alzheimer's drug, donepezil, markedly improves long-term survival after chronic heart failure in mice. J Card Fail 2009 ; 15 : 805.

6) Sato K, Urbano R, Yu C, et al. The effect of donepezil on cardiovascular mortality. Clin Pharmacol Ther 2010 ; 88 : 335.

7) Kakinuma Y, Akiyama T, Sato T. Cholinoceptive and cholinergic properties of cardiomyocytes involving an amplification mechanism for vagal efferent effects in sparsely innervated ventricular myocardium. FEBS J 2009 ; 276 : 5111.

8) Kakinuma Y, Furihata M, Akiyama T, et al. Donepezil, an acetylcholinesterase inhibitor against Alzheimer's dementia, promotes angiogenesis in an ischemic hindlimb model. J Mol Cell Cardiol 2010 ; 48 : 680.