

treatment at 3 to 5 mg/day suppressed cardiovascular mortality in patients with Alzheimer's disease.⁵ Moreover, the lower dosed donepezil still possess a cardioprotective effect on rat myocardial infarcted heart. Thus, the present results do not necessarily indicate that the dose of 5 mg·kg⁻¹·day⁻¹ is required for the treatment of human CHF.

The main objective of this study was to confirm the retrospective clinical finding⁵ about the protective effect of donepezil on cardiovascular mortality, to simply test the working hypothesis that chronic donepezil can improve the prognosis of CHF with an animal model, and not to clarify the mechanism. Therefore, cellular and molecular mechanisms for the beneficial effects of donepezil are little clarified in the present study. To establish the therapeutic strategy, further investigation on action sites, dose-dependent effects, and adverse effects of donepezil on CHF is required. And other cholinesterase inhibitors had severe side effects and therapeutic range was reported to be narrow (0.1 to 0.3 mg/kg, intraperitoneally) for in vivo mice model,³² unlike donepezil; therefore, we didn't perform further studies using those inhibitors.

Conclusion

The present study demonstrated that oral donepezil improved survival of CHF mice through prevention of pumping failure and cardiac remodeling. However, the mechanisms of anti-CHF actions of donepezil and the appropriate protocol for the treatment of CHF are still unsettled and should be investigated. To establish the therapeutic strategy shown in the present study, large-scale and long-term clinical trials are required as well as animal studies.

References

- Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation* 2004;109:120–4.
- Ando M, Katare RG, Kakinuma Y, Zhang D, Yamasaki F, Muramoto K, et al. Efferent vagal nerve stimulation protects heart against ischemia-induced arrhythmias by preserving connexin43 protein. *Circulation* 2005;112:164–70.
- Kakinuma Y, Ando M, Kuwabara M, Katare RG, Okudela K, Kobayashi 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;579:2111–8.
- Katate RG, Ando M, Kakinuma Y, Arikawa M, Handa T, Yamasaki F, 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* 2008;137:223–31.
- Sato K, Urbano R, Yu C, Yamasaki F, Sato T, Robertson D, et al. Protective effect of donepezil on cardiovascular mortality. [abstract]. *Circulation* 2008;117:e269.
- Scheuermann-Freestone M, Freestone NS, Langenickel T, Höhnel K, Dietz R, Willenbrock R. A new model of congestive heart failure in the mouse due to chronic volume overload. *Eur J Heart Fail* 2001;3: 535–43.
- Sutherland FJ, Shattock MJ, Baker KE, Hearse DJ. Mouse isolated perfused heart: characteristics and cautions. *Clin Exp Pharmacol Physiol* 2003;30:867–78.
- Sato T, Shishido T, Kawada T, Miyano H, Miyashita H, Inagaki M, et al. ESPVR of in situ rat left ventricle shows contractility-dependent curvilinearity. *Am J Physiol Heart Circ Physiol* 1998;274:H1429–34.
- Kameyama T, Chen Z, Bell SP, Fabian J, Lewinter MM. Mechanoelectric studies in isolated mouse hearts. *Am J Physiol Heart Circ Physiol* 1998;274:H366–74.
- Claessens TE, Georgakopoulos D, Afanasyeva, Vermeersch SJ, Millar HD, et al. Nonlinear isochrones in murine left ventricular pressure-volume loops: how well does the time-varying elastance concept hold? *Am J Physiol Heart Circ Physiol* 2006;290:H1474–83.
- Mirsky I, Tajimi T, Peterson KL. The development of the entire end-systolic pressure-volume and ejection fraction-afterload relations: a new concept of systolic myocardial stiffness. *Circulation* 1987;76:343–56.
- Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–8.
- Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293–302.
- Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–66.
- Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–21.
- Shinke T, Takeuchi M, Takaoka H, Yokoyama M. Beneficial effects of heart rate reduction on cardiac mechanics and energetics in patients with left ventricular dysfunction. *Jpn Circ J* 1999;63:957–64.
- Hu K, Naumann A, Fracarrolo D, Gaudron P, Kaden JJ, Neubauer S, et al. Heart rate reduction by zatebradine reduces infarct size and mortality but promotes remodeling in rats with experimental myocardial infarction. *Am J Physiol Heart Circ Physiol* 2004;286:H1281–8.
- Nishikimi T, Hagaman JR, Takahashi N, Kim HS, Matsuoaka H, Smithies O, et al. Increased susceptibility to heart failure in response to volume overload in mice lacking natriuretic peptide receptor-A gene. *Cardiovasc Res* 2005;66:94–103.
- Cox MJ, Hawkins UA, Hoit BD, Tyagi SC. Attenuation of oxidative stress and remodeling by cardiac inhibitor of metalloproteinase protein transfer. *Circulation* 2004;109:2123–8.
- Kamkin A, Kiseleva I, Wagner KD, Pylaev A, Leiterer KP, Theres H, et al. A possible role for atrial fibroblasts in postinfarction bradycardia. *Am J Physiol Heart Circ Physiol* 2002;282:H842–9.
- Shepherd G, Klein-Schwartz W, Edwards R. Donepezil overdose: a tenfold dosing error. *Ann Pharmacother* 1999;33:812–5.
- Bordier P, Garrigue S, Barold SS, Bressolles N, Lanusse S, Clémenty J. Significance of syncope in patients with Alzheimer's disease treated with cholinesterase inhibitors. *Europace* 2003;5:429–31.
- Vanhaesebroeck B, Alessi DR. The regulation and activities of the multifunctional serine/threonine kinase Akt/PKB. *Exp. Cell Res* 1999;253:210–29.
- Rogers SL. Perspectives in the management of Alzheimer's disease: clinical profile of donepezil. *Dement Geriatr Cogn Disord* 1998; 9(Suppl 3):29–42.
- Maurice T, Meunier J, Feng B, Ieni J, Monaghan DT. Interaction with sigma₁ protein, but not N-methyl-D-aspartate receptor, is involved in the pharmacological activity of donepezil. *J Pharmacol Exp Ther* 2006;317:606–14.
- Meunier J, Ieni J, Maurice T. The anti-amnesic and neuroprotective effects of donepezil against amyloid beta₂₅₋₃₅ peptide-induced toxicity in mice involve an interaction with the sigma₁ receptor. *Br J Pharmacol* 2006;149:998–1012.

27. Kato K, Hayako H, Ishihara Y, Marui S, Iwane M, Miyamoto M. TAK-147, an acetylcholinesterase inhibitor, increases choline acetyltransferase activity in cultured rat septal cholinergic neurons. *Neurosci Lett* 1999;260:5–8.
28. Novakova M, Ela C, Barg J, Vogel Z, Hasin Y, Eilam Y. Inotropic action of sigma receptor ligands in isolated cardiac myocytes from adult rats. *Eur J Pharmacol* 1995;286:19–30.
29. Kekuda R, Prasad PD, Fei YJ, Leibach FH, Ganapathy V. Cloning and functional expression of the human type 1 sigma receptor (hSigmaR1). *Biochem Biophys Res Commun* 1996;229:553–8.
30. Saxena G, Singh SP, Agrawal R, Nath C. Effect of donepezil and tacrine on oxidative stress in intracerebral streptozotocin-induced model of dementia in mice. *Eur J Pharmacol* 2008;581:283–9.
31. Auletta CS, Mitchell JM, Richter WR, Taki T, Sagami F. One-year oral toxicity study of donepezil hydrochloride in rats. *Jpn Pharmacol Ther* 1998;26(Suppl 6):S1177–95.
32. Akinci SB, Ulu N, Yondem OZ, Firat P, Guc MO, Kanbak M, Aypar U. Effect of neostigmine on organ injury in murine endotoxemia: missing facts about the cholinergic anti-inflammatory pathway. *World J Surg* 2005;29:1483–9.

In the Spotlight: BioInstrumentation



Ken-ichi Yamakoshi, *Member, IEEE*

I. INTRODUCTION

THE field of biomedical instrumentation continues to attract a considerable amount of research activity and effort worldwide in order to produce more convenient, reliable and useful apparatus for medical science. This covers numerous aspects of the field such as measurement principles and methodologies as well as transducers and instruments, with applications for diagnosis and/or health care. In this review, four topics are briefly introduced, based on recent publications in this area. These are: 1) ballistocardiography revisited; 2) current studies on noninvasive measurement of arterial blood pressure; 3) electrophysiological measurement with dry electrodes; and 4) recent advances in noninvasive optical measurement of blood constituents.

II. BALLISTOCARDIOGRAPHY REVISITED

Ballistocardiography is a measurement method based on the detection of the small change in body weight caused by the recoil of shifts in the center of mass of the blood ejected by ventricular contraction. The first report of the ballistocardiogram (BCG) measurement was in 1877 [1]. This is now considered as only a preliminary description, but, in 1936, Starr developed what is regarded as the epoch-making bed BCG measurement device [2]. Following this, many BCG studies were done over a three or four decade period, but, the use and study of BCG decreased in the latter half of the 1970s and then the method attracted little or no further scientific research interest in the field of biomedical engineering.

Ballistocardiography, however, is an attractive method due to the fact that it has the potential to allow truly noninvasive assessment of cardiac ejection function. This feature can be understood by considering the origin of the BCG as follows: As shown in Fig. 1(a), according to Newton's second law, the reaction force originating from blood ejection by ventricular contraction during the systolic period, $F(t)$, i.e., the BCG, is a derivative of the momentum, $P(t)$, ($F(t) = dP(t)/dt$). The momentum, $P(t)$, is the product of blood velocity, $v(t)$, in the ascending aorta and the mass of ejected blood, $m(t)$, where $m(t)$ is the product of ejected blood volume, $V(t)$, and blood density coefficient, ρ , i.e., $m(t) = \rho V(t)$. Therefore, $F(t)$ can be expressed by $F(t) = \rho d(v(t)V(t))/dt$. Then $V(t)$ is derived by integration of $v(t)$ during systole, and thus $F(t) = \rho d(v(t) \int v(t)dt)/dt$. If $v(t)$ is given as shown in the top panel of Fig. 1(b), then $F(t)$ can be calculated as shown in the bottom panel of Fig. 1(b). The pattern of the calculated $F(t)$ is quite similar to the measured BCG during systole, as shown in Fig. 1(c). Thus it can be seen that the BCG can contain information about cardiac ejection function.

In fact, several studies on BCG measurement have been made in this decade for the assessment of cardiac function. For example, we recently developed a new BCG monitor using a weighing scale with high resolution and accuracy that was installed in a toilet. This has successfully demonstrated BCG measurements, as well as the evaluation of cardiac functions such as cardiac output (CO), during the use of the toilet [3], [4]. More recently, the interest in BCG measurement has increased and further studies have been made by several groups. Inan *et al.* reported BCG measurement using subjects in a standing position and demonstrated a relatively low-cost BCG monitor that was based on a commercial scale [5], [6]. They also tried to estimate CO changes derived from the BCG. Recordings of BCGs from subjects after treadmill exercise were made and compared with CO changes determined by Doppler echocardiogram signals from the left ventricular outflow tract of the

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K.-I. Yamakoshi is with the Graduate School of Natural Science & Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan (e-mail: yamakosi@t.kanazawa-u.ac.jp).

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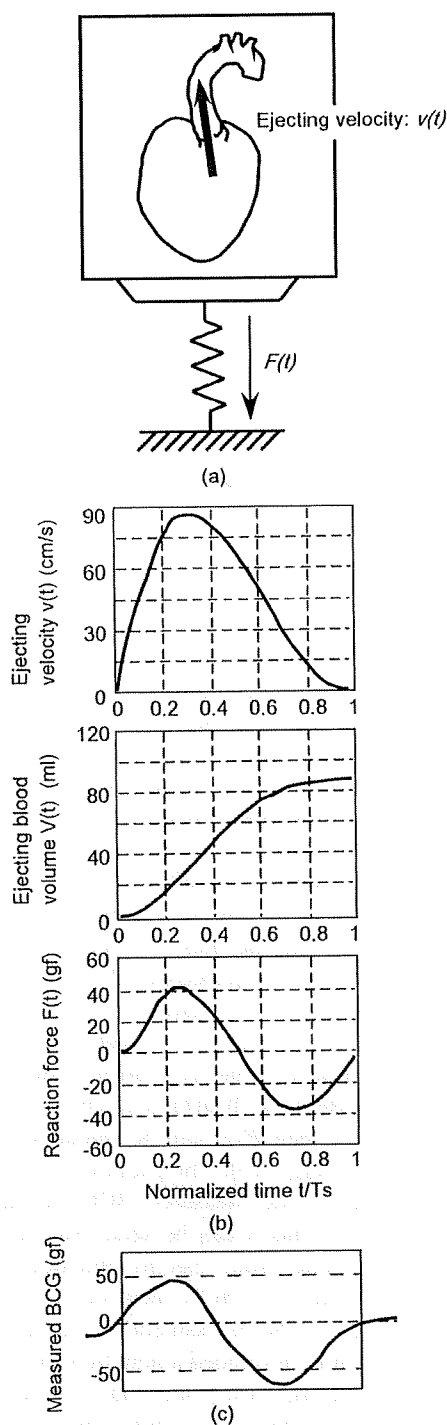


Fig. 1. Diagrammatic representation of the origin of the ballistocardiogram (BCG) (a), an example of numerical simulation showing ejecting velocity ($v(t)$), ejecting blood volume ($V(t)$) and calculated reaction force ($F(t)$) (b), and an example of measured BCG (c). Abscissa in (b) indicates time (t) normalized by systolic period (T_s). See text for further explanation.

heart. The results showed a relatively good correlation between them [7]. Han *et al.* developed an enhanced chair-type BCG measurement device implemented in a wheelchair and demonstrated BCG monitoring together with ECG in a disabled person [8], [9]. Mack *et al.* tried to measure BCG signals in bed to assess heart rate during sleep using a force sensor placed

beneath a bed sheet [10]. Chen *et al.* [11] and Motoi *et al.* [12] also demonstrated the BCG measurement during sleep using a flat-type sensor under a pillow.

Despite the increasing number of studies aimed at re-examining ballistocardiography, as described above, the method has still not become widely-accepted for clinical applications in the way that other methods such as ECG measurement have. Besides the need for new instruments using modern techniques, further clinical applications will need to be proven if the method is to recapture the past glory days.

III. CURRENT STUDIES ON NONINVASIVE MEASUREMENT OF ARTERIAL BLOOD PRESSURE

Noninvasive or indirect measurement of arterial blood pressure (BP) is an age-old topic and still of great importance in biomedical fields. Although several methods for noninvasive BP measurement have been proposed in the last two decades, validation studies against the gold standard of direct BP measurement with intra-arterial catheterization, have been lacking. Recently, Chemla *et al.* provided a review of recent advances in noninvasive BP measurement in the field of critical care [13]. These authors have drawn an important conclusion that in hemodynamically unstable patients when critical decisions are required direct BP measurement is preferred over noninvasive methods. Furthermore they also concluded that current commercially available BP instruments based on the auscultatory and/or cuff-oscillometric method may provide valuable information only for hemodynamically stable patients.

Advances in the field of noninvasive BP measurement are still required, either through further improvements to existing techniques or by means of entirely novel approaches. Within this context, Muehlsteff *et al.* tried to estimate BP by the use of a conventional pulse arrival time method [14]. Shin *et al.* reported the measurement of systolic BP from the BCG and compared the resulting BP values with those derived by Finapres, a commercially available BP monitor [15]. Suzuki *et al.* attempted to estimate BP by analyzing photoplethysmographic signals and the BP values were compared with those from a commercial cuff-oscillometric type BP monitor [16]. A new cuff-less BP measuring method based on hydrostatic pressure has been proposed by Shaltis *et al.*, results being compared with data from a Finapres monitor [17].

Despite these new approaches, it is noted that in the reported studies no definitive evaluations were made by comparison with the direct BP measurement. As previously reported, the auscultatory and cuff-oscillometric BP values tend to provide a significant underestimation as compared to intra-arterial BP values [18], [19]. Moreover, the reason for this difference is still unclear and remains under discussion [20]. The discrepancy is most likely to be caused by both practical and theoretical problems of these noninvasive BP measurement techniques [21], [22]. In order for the field to advance, further scientifically rigorous investigations, in which noninvasive BP measurements are compared to direct BP measurement as the gold standard, will be required in order to achieve methods with high accuracy and reliability.

IV. ELECTROPHYSIOLOGICAL MEASUREMENTS WITH DRY ELECTRODES

There continue to be attempts to replace or complement the conventional pre-gelled electrode, used widely for research and clinical electrophysiological measurement, with so-called dry-electrodes. During the year since the previous review of "recent advances" of such electrodes [23] some further attempts of new dry electrode designs have been appeared. For example, Chi *et al.* developed a coin-sized non-contact capacitive biopotential electrode with a low-power amplifier (940 μ W) and ECG measurement through clothes was successfully demonstrated [24]. Ng *et al.* developed a novel dry electroencephalography electrode with many micro-spikes of about 6 μ m diameter and 110 μ m length [25]. The micro-spike can penetrate the stratum corneum of the epidermidis and thereby improve electrical conductivity at the skin-electrode interface. These authors also discussed a mass production technology for the electrode employing a vacuum casting process that can allow lower-cost mass production than other methods such as the conventional electrodeposition forming or the LIGA (Lithographie, Galvanoformung, Abformung) process.

A highly interesting and noteworthy dry electrode as an alternative to the conventional gelled electrodes has been reported by Prance *et al.* [26]. They have demonstrated a new approach to electrophysiological measurement using a capacitive electrode, comprising of an ultrahigh impedance electric potential sensor. This has an input capacitance of 10 fF, and an input resistance of $10^{15} \Omega$. The sensor characteristics allowed the measurement of the electric field around a human body at a distance of up to 40 cm, showing that a waveform synchronized with the ECG was clearly obtained remotely from a human body *via* a 10 cm air-gap. The waveform obtained with a 40 cm air-gap was noisier than that with a 10 cm gap, but the cardiac component could still be observed. This sensor could also detect respiration signals remotely with a 40 cm air-gap. Although the waveforms obtained with this method have remained somewhat ill-defined, this completely non-contact monitoring approach could have the potential to evolve into an important new physiological measurement methodology.

V. RECENT ADVANCES IN NONINVASIVE OPTICAL MEASUREMENT OF BLOOD CONSTITUENTS

Noninvasive *in vivo* blood constituent measurement has a long history since the first attempts at oximetry by Millikan in 1942 [27]. Pulse oximetry invented by Aoyagi using a photo-plethysmograph (PPG) with two [28] or three wavelengths [29] to measure oxygen saturation in arterial blood is undoubtedly an epoch-making example of optical measurement. Over the years, several new attempts at *in vivo* blood constituent measurement were reported. Ogawa *et al.* demonstrated a new calibration method for pulse oximetry without using the conventional ratio of absorptions, the approach being based on the use of a nonlinear regression with Support Vector Machines (SVMsR) [30]. Although the present pulse oximeter is widely used in clinical practice and many efforts have been made focusing on miniaturization, motion artifact rejection and so on, it should

be noted that there still remain several practically problematic difficulties, particularly on calibration procedures. The use of SVMsR may be feasible to solve such calibration procedures.

Besides the use of the PPG for oxygen measurement as achieved with pulse oximetry, other optical techniques to measure blood constituents have been anticipated. Recently, pulse carbon monoxide oximetry, named "pulse CO-oximetry," has been proposed and substantiated in clinical use [31], [32]. It is also noted that "pulse glucometry" with a very high speed near-infrared spectrophotometer for the measurement of blood glucose, which was introduced in the previous review [23], has also now been combined with SVMsR and nonlinear classification analyses to achieve substantive results for the practical use of this method [33].

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REFERENCES

- [1] J. W. Gordon, "Certain molar movements of the human body produced by the circulation of the blood," *J. Anat. Physiol.*, vol. 11, pt. 3, pp. 533–536, 1877.
- [2] I. Starr and F. C. Wood, "Twenty-year studies with the ballistocardiograph, the relation between the amplitude of the first record of "healthy" adults and eventual mortality and morbidity from heart disease," *Circulation*, vol. 23, no. 5, pp. 714–732, 1961.
- [3] K. Yamakoshi, "Unconstrained physiological monitoring in daily living for health care," *Front. Med. Biol. Eng.*, vol. 10, no. 3, pp. 239–259, 2000.
- [4] K. Motoi, S. Kubota, A. Ikarashi, M. Nogawa, S. Tanaka, T. Nemoto, and K. Yamakoshi, "Development of a fully automated network system for long-term health-care monitoring at home," in *Proc. 29th IEEE EMBS Annu. Conf.*, 2007, pp. 1826–1829.
- [5] O. T. Inan, M. Etemadi, R. M. Wiard, G. T. A. Kovacs, and L. Giovanngrandi, "Non-invasive monitoring of valsalva-induced hemodynamic changes using a bathroom scale ballistocardiograph," in *Proc. 30th Annu. IEEE Engineering in Medicine and Biology Conf.*, 2008, pp. 674–677.
- [6] O. T. Inan, M. Etemadi, A. Paloma, L. Giovanngrandi, and G. T. Kovacs, "Non-invasive cardiac output trending during exercise recovery on a bathroom-scale-based ballistocardiograph," *Physiol. Meas.*, vol. 30, no. 3, pp. 261–274, Mar. 2009.
- [7] O. T. Inan, M. Etemadi, R. M. Wiard, L. Giovanngrandi, and G. T. Kovacs, "Robust ballistocardiogram acquisition for home monitoring," *Physiol. Meas.*, vol. 30, no. 2, pp. 169–185, Feb. 2009.
- [8] D. K. Han, J. M. Kim, E. J. Cha, and T. S. Lee, "Wheelchair type biomedical system with event-recorder function," in *Proc. 30th IEEE EMBS Annu. Conf.*, 2008, pp. 1435–1438.
- [9] D. K. Han, J. M. Kim, J. H. Hong, E. J. Cha, and T. S. Lee, "Performance evaluation of biosignal measurement at the wheelchair system," in *Proc. 30th IEEE EMBS Annu. Conf.*, 2008, pp. 1451–1454.
- [10] D. C. Mack, J. T. Patrie, P. M. Suratt, R. A. Felder, and M. A. Alwan, "Development and preliminary validation of heart rate and breathing rate detection using a passive, ballistocardiography-based sleep monitoring system," *IEEE Trans. Inf. Technol. Biomed.*, vol. 13, no. 1, pp. 111–120, Jan. 2009.
- [11] W. Chen, X. Zhu, T. Nemoto, K. Kitamura, K. Sugitani, and D. Wei, "Unconstrained monitoring of long-term heart and breath rates during sleep," *Physiol. Meas.*, vol. 29, no. 2, pp. N1–10, Feb. 2008.
- [12] K. Motoi, M. Ogawa, H. Ueno, Y. Kuwae, A. Ikarashi, T. Yuji, Y. Higashi, S. Tanaka, T. Fujimoto, H. Asanoi, and K. Yamakoshi, "A fully automated health-care monitoring at home without attachment of any biological sensors and its clinical evaluation," in *Proc. 31st IEEE EMBS Annu. Conf.*, Sep. 2009, pp. 4323–4326.
- [13] D. Chemla, J. L. Teboul, and C. Richard, "Noninvasive assessment of arterial pressure," *Curr. Opin. Crit. Care.*, vol. 14, no. 3, pp. 317–321, Jun. 2008.

- [14] J. Muehlsteff, X. A. Aubert, and G. Morren, "Continuous cuff-less blood pressure monitoring based on the pulse arrival time approach: The impact of posture," in *Proc. 30th IEEE EMBS Annu. Conf.*, 2008, pp. 1691–1694.
- [15] J. H. Shin, K. M. Lee, and K. S. Park, "Non-constrained monitoring of systolic blood pressure on a weighing scale," *Physiol. Meas.*, vol. 30, no. 7, pp. 679–693, July 2009.
- [16] S. Suzuki and K. Oguri, "Cuffless and non-invasive systolic blood pressure estimation for aged class by using a photoplethysmograph," in *Proc. 30th IEEE EMBS Annu. Conf.*, 2008, pp. 1327–1330.
- [17] P. A. Shaltis, A. T. Reisner, and H. H. Asada, "Cuffless blood pressure monitoring using hydrostatic pressure changes," *IEEE Trans. Biomed. Eng.*, vol. 55, no. 6, pp. 1775–1777, Jun. 2008.
- [18] F. H. Van Bergen, D. S. Weatherhead, A. E. Treloar, A. B. Dobkin, and J. J. Buckley, "Comparison of indirect and direct methods of measuring arterial blood pressure," *Circulation*, vol. 10, no. 4, pp. 481–490, Oct. 1954.
- [19] A. Bur, M. M. Hirschl, H. Herkner, E. Oschatz, J. Kofler, C. Woisetschlager, and A. N. Laggner, "Accuracy of oscillometric blood pressure measurement according to the relation between cuff size and upper-arm circumference in critically ill patients," *Crit. Care Med.*, vol. 28, no. 2, pp. 371–376, Feb. 2000.
- [20] J. N. Amore, Y. Lemesre, I. C. Murray, S. Mieke, S. T. King, F. E. Smith, and A. Murray, "Automatic blood pressure measurement: The oscillometric waveform shape is a potential contributor to differences between oscillometric and auscultatory pressure measurements," *J. Hypertens.*, vol. 26, no. 1, pp. 35–43, Jan. 2008.
- [21] K. Yamakoshi, P. A. Oberg, T. Togawa, and F. Spelman, Eds., "Non-invasive cardiovascular haemodynamic measurements," in *Sensors in Medicine and Health Care*. Weinheim, Germany: Wiley-VCH Verlag, 2004, vol. 3, pp. 107–160, (Sensors Applications).
- [22] K. Yamakoshi, "Volume-compensation method for non-invasive measurement of instantaneous arterial blood pressure—Principle, methodology, and some applications," *Homeostasis*, vol. 36, no. 2–3, pp. 90–119, 1995.
- [23] K. Yamakoshi, "In the spotlight: BioInstrumentation," *IEEE Rev. Biomed. Eng.*, vol. 1, pp. 2–3, 2008.
- [24] Y. M. Chi, S. R. Deiss, and G. Cauwenberghs, "Non-contact low power EEG/ECG electrode for high density wearable biopotential sensor networks," in *Proc. Sixth Int. Workshop on Wearable and Implantable Body Sensor Networks*, 2009, pp. 246–250.
- [25] W. C. Ng, H. L. Seet, K. S. Lee, N. Ning, W. X. Tai, M. Sutedja, J. Y. H. Fuh, and X. P. Li, "Micro-spike EEG electrode and the vacuum-casting technology for mass production," *J. Materials Processing Technology*, vol. 209, no. 9, pp. 4434–4438, May 2009.
- [26] R. J. Prance, S. T. Beardsmore-Rust, P. Watson, C. J. Harland, and H. Prance, "Remote detection of human electrophysiological signals using electric potential sensors," *Appl. Phys. Lett.*, vol. 93, no. 2, p. 033906, 2008.
- [27] G. A. Millikan, "The oximeter, an instrument for measuring continuously the oxygen saturation of arterial blood in man," *Rev. Sci. Instrum.*, vol. 13, pp. 434–444, 1942.
- [28] T. Aoyagi and K. Miyasaka, "Pulse oximetry: Its invention, contribution to medicine, and future tasks," *Anesth. Analg.*, vol. 94, no. 1, pp. S1–3, Jan. 2002, Suppl.
- [29] T. Aoyagi, M. Fuse, N. Kobayashi, K. Machida, and K. Miyasaka, "Multiwavelength pulse oximetry: Theory for the future," *Anesth. Analg.*, vol. 105, no. 6, pp. S53–8, Dec. 2007, Suppl. tables of contents.
- [30] M. Ogawa, Y. Yamakoshi, M. Nogawa, T. Yamakoshi, K. Motoi, S. Tanaka, and K. Yamakoshi, "A new calibration method with support vector machines for pulse oximetry," in *Proc. 4th Eur. Conf. IFMBE*, Nov. 2008, pp. 1125–1127.
- [31] S. Suner and J. McMurdy, "Masimo rad-57 pulse co-oximeter for noninvasive carboxyhemoglobin measurement," *Expert Rev. Med. Devices*, vol. 6, no. 2, pp. 125–30, Mar. 2009.
- [32] S. J. Barker, J. Curry, D. Redford, and S. Morgan, "Measurement of carboxyhemoglobin and methemoglobin by pulse oximetry: A human volunteer study," *Anesthesiol.*, vol. 105, no. 5, pp. 892–897, Nov. 2006.
- [33] Y. Yamakoshi, M. Ogawa, and T. Tamura, "Multivariate regression and classification models for estimation of blood glucose levels using a new non-invasive optical measurement technique named "pulse-glucometry"," *The Open Optics J.*, vol. 3, pp. 63–69, Sep. 2009.

容積振動型血圧計測法の高精度化に関する研究

日下部朋哉* 野川雅道 山越健弘 田中志信 山越憲一

*金沢大学 自然科学研究科, 金沢大学 理工研究域

〒920-1192 金沢市角間町 Phone/Fax:076-234-4760

あらまし 無侵襲血圧計測法である容積振動法(間欠法)の高精度化に関して研究を行っている。今回、血管の圧-容積曲線に基づいた最高・最低血圧の決定方法を開発することにより、精度の向上を直接血圧計(Bland-Altman plot (\pm SD))において最高血圧誤差 2.3 ± 7.7 [mmHg],最低血圧誤差 -1.8 ± 6.4 [mmHg], $n=2$)において確認した。本法の開発により、容積振動法の精度が向上した。

キーワード 血圧計測, 容積振動法, 血管圧-容積関係

Improvement of volume-oscillometric noninvasive blood pressure measurement method

Tomoya KUSAKABE*, Masamichi NOGAWA, Takehiro YAMAKOSHI, Shinobu TANAKA and Ken-ichi YAMAKOSHI

*Kanazawa University, Graduate School of Natural Science & Technology
Kanazawa University, College of Science and Engineering

Kanazawa city, Kakuma-machi, 920-1192, JAPAN

Abstract A novel intermittent noninvasive blood pressure measurement method based on vascular unloading technique has been developed to determine systolic and diastolic blood pressure (SBP, DBP) with clear physical assumption. The accuracy of the method was evaluated through the direct blood pressure measurement method. The Bland-Altman plots (\pm SD) of the SBP, 2.3 ± 7.7 [mmHg], and DBP, -1.8 ± 6.4 [mmHg] were obtained. The novel blood pressure measurement method has been well demonstrated with high accuracy.

Keywords: blood pressure, volume-oscillometric method, vascular-unloading technique

1. まえがき

我が国において高齢化率の上昇や不適切な生活習慣により、高血圧人口が増加傾向にある。慢性的な高血圧は動脈硬化を引き起こし、その結果、循環器系疾患となる可能性が高いことから、血圧を日常的に計測・管理し、正常な値に保つことが大切である。一般的に使用されている無侵襲間欠式血圧計測法であるカフ振動法は、平均血圧に対応するカフ内圧の振幅最大点を基準にして、その振幅の減衰比から、最高・最低血圧を決定しているが、その振幅の減衰比などの具体的な値は、経験的・統計的に決定していることから、物理的な背景が明確にされないまま使用されているのが現状である。一方、間欠式血圧計測法である容積振動法においては、平均血圧に対応する血管容積変化(容積脈波)の振幅最大点および、消失点・出現点を最高血圧として決定出来る利点があるが[1,2]、最低血圧に関しては、いくつかの提案が行われているが、簡単には決定が困難であった[3,4]。

そこで、本研究では、従来の容積振動法を再検討することで、測定原理が物理的・力学的に明確な最高・平均・最低血圧の新たな決定法を開発したので報告する。

2. 容積振動法の改良

間欠式血圧計測法である容積振動法は、図1に示す血管の力学特性である圧-容積曲線に基づいて、血管内外圧の平衡点である平均血圧に対応する血管容積 V_0 を血管容積振動(容積脈波)の振幅最大点から決定する[1,2]。ここで、図1に示すように血管容積変化(dV/dP_c)の最大点を V_0 として捕らえなおすことが可能である。この原理を最高(DBP)・最低血圧(SBP)の平衡点にも適用して考えると、図2に示す新たな血圧計測原理を提案することが可能である。本研究では、血管容積を光電容積信号として検出することから、光電的に検出する無負荷時血管容積(V_0)を PG_{V_0} と表記する。

具体的には、一拍毎の脈波ボトム(PG_D)及び脈波ピーク(PG_S)とそれらに対応する外圧(P_c)を検出し、圧-容積関係に基づいたエンベロープを描き、そこで外圧に対する血管容積変化(dV/dP_c)を適用すると、血管容積変化の最大点に対応する血管容積が最低血圧(DBP)及び最高血圧(SBP)時の無負荷時血管容積であると考えられ、それぞれの血管容積を PG_{V_0-D} 及び PG_{V_0-S} と名付けることとした。理想的な血管状態を考慮すると PG_{V_0-D} , PG_{V_0-S} , PG_{V_0} は全て一致すると考えられる。この PG_{V_0-D} , PG_{V_0-S} 及び PG_{V_0} のパラメータの関係から適切な血圧決定法について検討を行った。

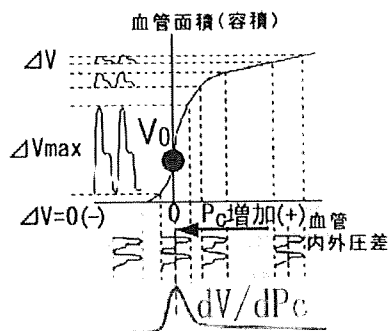


図1 動脈の力学特性(圧-容積曲線)

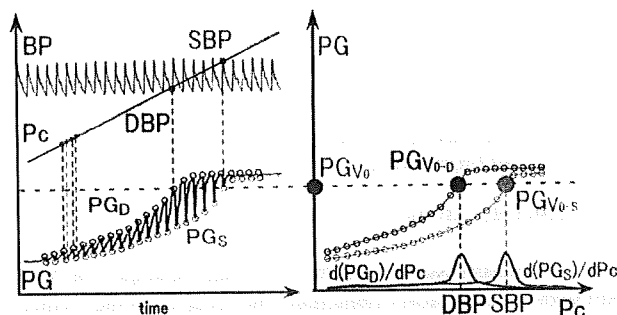


図2 新規容積振動法の原理

3. 試作無侵襲手首血圧計測システム

図3に本研究で用いた試作無侵襲手首血圧計測システムの概要図を示す。LEDとフォトダイオード(PD)を用いた光センサにより、血管容積を光電的に検出し、光電容積(PG)やカフ圧(P_c)をDSP Board(DS1104; dSPACE GmbH, ドイツ)を介してA/D変換を行う。Matlab/Simlinkで作成したコントローラを実装したDSPからD/A変換を行い、電空変換器(EPC)へ信号が送られ、 P_c を制御することで、血管容積を制御している。手首固定具はラチェット式で、片手で装着可能である。固定具には圧力センサやEPCが一体化しており、カフ圧を瞬時に制御可能である。

4. 実験方法

被験者は2名を対象とし、右手首に本システム、左手首に直接法を適用した。実験後の容積振動法の解析により PG_{V0} 、 PG_{V0-D} 、 PG_{V0-S} を取得した。左手首では直接血圧値を計測した。尚、本実験は金沢大学医学系倫理審査委員会の承認を経て実施した。

5. 実験結果

図4に実験結果例を示す。図4の右側は外圧に対する血管容積変化 dPG/dP_c のグラフで、それぞれのピークに対応

するカフ圧は、SBPが122mmHg、DBPが78mmHgであった。また、容積振動法中の直接血圧値BPはSBPが128mmHg、DBPが77mmHgであり、容積振動法におけるSBP及びDBPが良好に計測できた。同時に取得した PG_{V0-D} 、 V_0 及び PG_{V0-S} は $PG_{V0-D} \leq V_0 \leq PG_{V0-S}$ の関係を満たしていた。

図5は直接法と容積振動法から取得したSBP及びDBと直接血圧値を評価した結果である。全データから、 PG_{V0-D} 、 PG_{V0} 及び PG_{V0-S} が $PG_{V0-D} \leq PG_{V0} \leq PG_{V0-S}$ の関係を満たすデータを抽出すると、Bland-Altman plotにおいて、DBPに関しては平均誤差 $\pm SD = -1.8 \pm 6.4$ [mmHg]、SBPに関しては平均誤差 $\pm SD = 2.3 \pm 7.7$ [mmHg]であり、直接法と比較して最も良好な値を取得できた。即ち容積振動法において PG_{V0-D} 、 PG_{V0} 及び PG_{V0-S} が $PG_{V0-D} \leq PG_{V0} \leq PG_{V0-S}$ の関係を満たす時、適切な PG_{V0} を計測出来ると考えられる。 PG_{V0-D} 、 PG_{V0} 及び PG_{V0-S} が全て一致しないのは、血管壁の粘性に由来するヒステリシスに起因するものと考えられる。

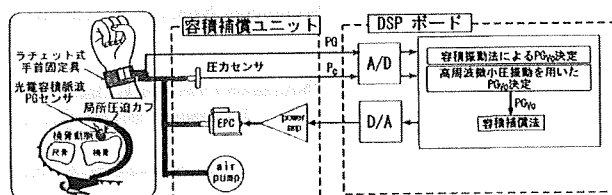


図3 試作手首血圧計測システム概要図

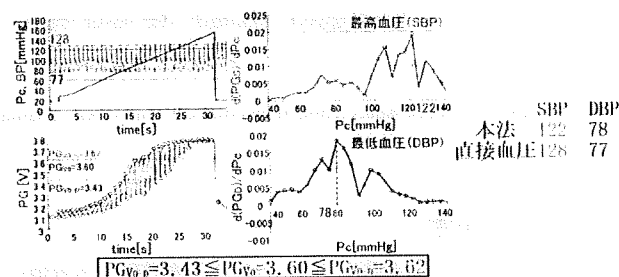


図4 手首容積振動法計測結果例

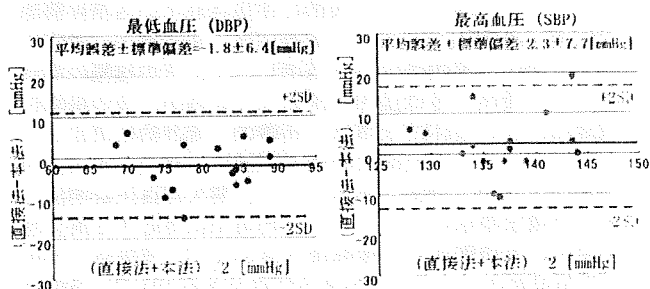


図5 Bland-Altman plotによる手首容積振動法のDBP, SBPと直接血圧値の評価

6. 結言

本研究では、容積振動法の改良法を提案し、容積振動法実施時に取得した圧力変化に対する血管容積変化の3種類の最大点 PG_{V0-D} , PG_{V0} 及び PG_{V0-S} が $PG_{V0-D} \leq PG_{V0} \leq PG_{V0-S}$ の関係を満たす時に、DBP 及び SBP は直接血圧値と良好に一致することを確認した。

参考文献

- [1] Yamakoshi K, Shimazu H, Shibata M, Kamiya A., New oscillometric method for indirect measurement of systolic and mean arterial pressure in the human finger. Part 1: model experiment., Med Biol Eng Comput. May;20(3):307-13, 1982
- [2] Yamakoshi K, Shimazu H, Shibata M, Kamiya A., New oscillometric method for indirect measurement of systolic and mean arterial pressure in the human finger. Part 2: correlation study., Med Biol Eng Comput. May;20(3):314-8, 1982
- [3] Shimazu H, Ito H, Kobayashi H, Yamakoshi K., Idea to measure diastolic arterial pressure by volume oscillometric method in human fingers., Med Biol Eng Comput. Sep;24(5):549-54, 1986
- [4] Shimazu H, Ito H, Kwarada A, Kobayashi H, Hiraiwa A, Yamakoshi K., Vibration technique for indirect measurement of diastolic arterial pressure in human fingers., Med Biol Eng Comput. Mar;27(2):130-6., 1989

