Losing harmonic stability of arterial pulse in terminally ill patients

Yu-Cheng Kuo[a,b], Tai-Yuan Chiu[c], Ming-Yie Jan[d], Jian-Guo Bau[d], Sai-Ping Li[d], Wei-Kung Wang[b,d] and Yuh-Ying Lin Wang[d,e]

Objective To measure the coefficient of variation of the harmonic magnitude (HCV) of the radial arterial pulse before death of cancer patients.

Methods We non-invasively recorded the radical arterial pulse of 21 end-stage cancer patients, 31 healthy subjects, and 47 outpatient department (OPD) patients. During the 2-week study, eight cancer patients expired.

Results There were no considerable differences in diastolic or systolic blood pressure between cancer patients and other subjects; however, all six HCVs were significantly higher in the cancer patients ($P<0.05$). Within the cancer patient group, the first and second HCV were notably higher in the patients that expired ($P<0.05$), and the first to fourth HCVs were significantly increased on their last day ($P<0.05$). In the control healthy subjects and the OPD group, the HCVs were below 5 and 8%, respectively. In the cancer patients, the third to sixth HCVs were higher than 15%. On the last day of the cancer patients that expired, even the first and second HCVs were higher than 15%.

Conclusions During the dying process, the traditional diastolic and systolic blood pressure did not show significant changes; however, all the harmonic components gradually lost their stability. The HCVs, which increased first for the high-frequency components and then the low-frequency components, could quantitatively reflect the severity of different stages of illness. _Blood Press Monit_ 9:255–258 © 2004 Lippincott Williams & Wilkins.

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[a]Institute of Pharmacology, Taipei Medical University, Taipei, [b]Department of Electric Engineering, National Taiwan University, Taipei, [c]Hospice and Palliative Care Unit, National Taiwan University Hospital, Taipei, [d]Biophysic Laboratory, Institute of Physics, Academia Sinica, Taipei and [e]Department of Physics, National Taiwan Normal University, Taipei, Taiwan.

Correspondence and requests for reprints to Yuh-Ying Lin Wang, Biophysic Laboratory, Institute of Physics, Academia Sinica Nankang, Taipei, Taiwan.
Tel: +886 (2) 27880058 2050; fax: +886 (2) 27834187;
email: wkwang@phys.sinica.edu.tw

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Introduction

As Glass stated, ‘Physiological rhythms are central to life. Disruption of rhythmic processes beyond normal bounds or emergence of abnormal rhythms is associated with disease’ [1]. Indeed, death is the termination of all physiological rhythms. Is there a biological rhythm that reflects most diseases and is associated with the dying process? It must be the fundamental component of the physiological rhythms.

In both philosophy and medicine, death is a major issue. The questions ‘Will this patient die?’ and ‘When will this patient die?’ are some of the most difficult questions that doctors face. Sudden death is even more troublesome. However, these unavoidable problems and risks must be seriously addressed in intensive care units, ambulances, emergency wards, anaesthetized patients undergoing surgery, and patients in hospices who have end-stage cancer. Because the answers to these questions affect the course of treatment as well as the feelings of the patients’ families, there are broad implications for them in medical economics and society [2,3].

Nevertheless, the accurate forecasting of death is not an easy matter, and many predictive systems have been formulated. These include the assessment of patients’ condition near death [3–6], Simplified Acute Physiology (SAPS) scores [2], Mortality Probability Model (MPM) scores [2,7], Palliative Prognostic Index (PPI) scores [8], Acute Physiology and Chronic Health Evaluation (APACHE) scores [9], and even the use of neural networks to assist prediction [10]. Most of these predictive systems are qualitative, so there are differences in accuracy, limits due to technique, or variance due to ethnic differences [9,11]. Thus, to establish a broad and accurate system to forecast death, an objective quantitative indicator is needed.

Blood pressure, heart rate, arterial oxygen concentration, body temperature, and breath rate are frequently used as physiological quantitative indicators of death. These vital signs cannot provide enough information, however, because they are usually kept within normal range by the intervention of treatment. Thus, the advanced

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analysis of these quantitative vital signs has become a new direction of research [12,13]. Heart rate variability has been the most successful quantitative indicator so far [14,15]. It has been extensively studied in cardiac and brain death [16–19]. Research has been widely applied in clinical situations to evaluate prognosis and outcome [18–23]. Some studies combined blood pressure with heart rate variability and obtained complements to diagnosis [17,24]. However, there is little information on blood pressure variability during the dying process in cancer patients specifically [25]. Can decoding the fluctuations in physiological rhythms fully answer questions regarding the dying process?

The importance of information within arterial pulse waves has been recognized in clinical medicine for a long time [26]. Arterial pulse wave analysis has been used widely in clinical practice, such as in hypertension, cardiac failure, and aging [27]. Previously, we found that the coefficient of variation of the harmonic magnitude (HCV) of caudate arterial pulse was raised significantly during the dying process in rats [28], and the HCV of arterial pulse increased before the fatal drop of blood pressure. We propose that HCV could be a good indicator to forecast the approach of death. This study was conducted on humans to confirm the proposal.

Methods

End-stage cancer patients admitted to the Hospice and Palliative Care Unit of National Taiwan University Hospital were recorded during the 2-week study. The experiments were conducted with the permission of patients or their family, and the responsible ethical committee has approved the experiments. Non-invasive pulse pressure of the radical artery was obtained once daily between 1500 and 1800 h by a pressure transducer (PSL-200GL; Kyowa Electronic Instrument Co. Ltd., Minato-ku, Tokyo, Japan). The device was fixed on the skin by scotch tape and an adjustable belt with a small button to give suitable pressure on the transducer. Our criterion of a good measurement was to seek the largest amplitude of the pulse [29]. As a control group, we also recorded 31 healthy subjects without obvious symptoms and 47 outpatient department (OPD) patients.

The output of the transducer was connected to an IBM PC for analysis via an A/D converter with sampling rate = 250 datapoints/s. The pulse spectrum was analysed with the Fourier transformation using T (period) = 1 pulse time [30].

After Fourier transformation, we analysed the first six harmonic magnitudes [31]. Each measurement recorded 8 s and contained 4–15 whole pulses. The mean value of the magnitude and the standard deviation of each harmonic were calculated. The coefficient of variation equals the standard deviation divided by the mean.

We then compared the HCV of the first six components within each group [32]. We also used the coefficient of variation to analyse the stability of each harmonic component, taking 15% as the threshold. If the coefficient of variation of a harmonic component was higher than 15%, we regarded the harmonic component as having lost stability.

Results

During the study, we recorded the pulse pressure of 21 end-stage cancer patients. Among them, eight persons expired, five females and three males. The age and blood pressure of the healthy subjects, the OPD patients, and the end-stage cancer patients are summarized in Table 1.

After Bonferroni *t*-tests were performed, we found that there were no significant differences in age, systolic blood pressure, and diastolic blood pressure between the healthy subjects and the OPD patients; however, the sixth HCV was significantly higher in the OPD patients (Bonferroni *t*-test, $P < 0.05$; Fig. 1). Between the OPD patients and the end-stage cancer patients, there were no significant differences in age, systolic blood pressure, and diastolic blood pressure; however, all the HCVs were significantly higher in the end-stage cancer patients than in the OPD patients (Bonferroni *t*-test, $P < 0.05$; Fig. 1). Comparing the data of the 13 living and the eight expired end-stage cancer patients, there were no significant differences in age, systolic blood pressure, and diastolic blood pressure; however, the first and second HCV values were significantly higher in the end-stage cancer patients that expired (Bonferroni *t*-test, $P < 0.05$; Fig. 1).

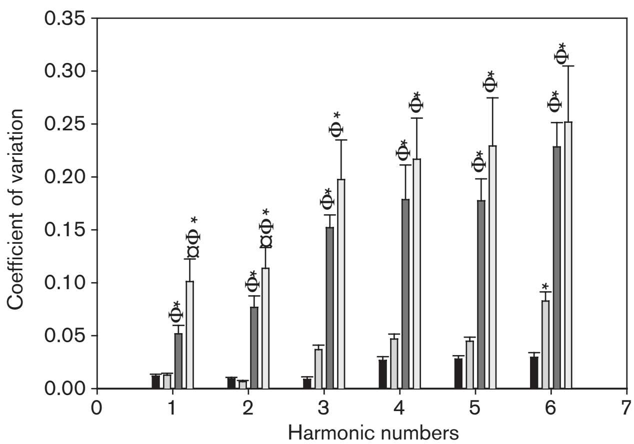
Looking more closely at the last 2 days of those end-stage cancer patients that expired, we found that the first to fourth HCVs increased significantly on the last day as compared with those recorded one day before (paired *t*-test, $P < 0.05$; Fig. 2), even though there were no significant changes in the systolic and diastolic blood pressures.

Table 1 Age and blood pressure of healthy subjects, OPD patients, and end-stage cancer patients

	Age	SP	DP
Healthy subjects (*n*=31)	62.1 ± 2.3	115.1 ± 2.2	72.7 ± 1.5
OPD patients (*n*=47)	65.2 ± 1.4	115.5 ± 2.9	70.5 ± 1.5
Cancer patients (*n*=21)	63.4 ± 4.4	116.0 ± 3.1	70.8 ± 1.7
Lived (*n*=13)	61.8 ± 6.0	115.8 ± 3.9	71.2 ± 2.2
Expired (*n*=8)	66.0 ± 6.5	116.2 ± 5.6	70.1 ± 3.0
Last day (*n*=7)	66.0 ± 7.5	117.3 ± 13.3	67.7 ± 7.4
Second to last day (*n*=7)	66.0 ± 7.5	107.9 ± 6.5	68.0 ± 6.3

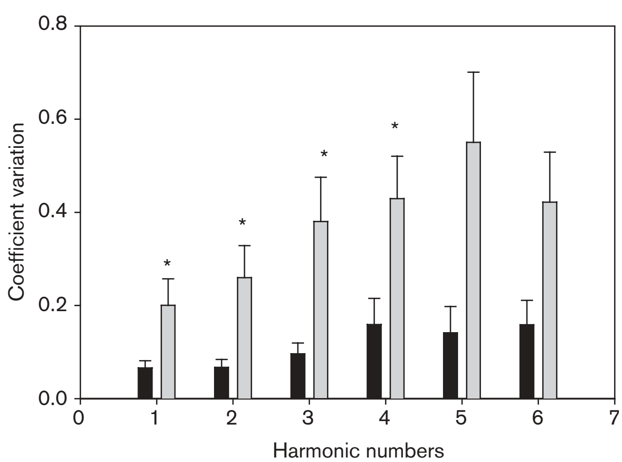
n, number of subjects; OPD, outpatient department. Data are age, systolic blood pressure (SP), and diastolic blood pressure (DP). Values are means ± SE.

Fig. 1



Coefficient of variation of harmonic components in the healthy subjects (n=31), outpatient department (OPD) patients (n=47), the living end-stage cancer patients (n=13), and the expired end-stage cancer patients (n=8). Values are means ± SE. Black bars represent healthy subjects, grey bars represent OPD patients, dark grey bars represent the living end-stage cancer patients, and light grey bars represent the expired end-stage cancer patients. n, number of subjects. Between symbols such as * and $P<0.05$ versus healthy subjects. Φ and $P<0.05$ versus OPD patients. □ and $P<0.05$ versus the living end-stage cancer patients.

Fig. 2



Coefficient of variation of harmonic components in expired cancer patients (n=7). Black bars represent the second to last day and grey bars represent the last day. Values are means ± SE. n, number of subjects. Between symbol such as * and $P<0.05$.

When we analysed the stability of the harmonic components, we found that in the control healthy subjects the HCVs were all below 5%. The HCVs of the OPD patients were all below 8%. In the cancer patients, only the first and the second HCVs were less than 15%, while the third to sixth HCVs exceeded 40% (i.e., lost their stability). On the last day of those cancer patients that expired, even the first and second HCVs were higher than 15%; that is, all harmonic components lost stability on the day of expiration, reflecting the failure of the circulatory system during the dying process.

Discussion

During the study, only eight persons expired in the hospital. According to Taiwanese social customs, people don't want themselves or family members to die in the hospital. Some patients were taken home before death, and we could not record their pulses. One of the cancer patients expired in the hospital within 1 day of admission. We included this data in the Bonferroni t-test, but in the paired t-test it was excluded.

Similar to the dying process of rats, the HCVs increased during the dying process of the end-stage cancer patients. In our previous experiments with rats, the dying process was initiated by injecting fatal doses of anaesthesia and the data were recorded every minute. In this experiment, we chose patients in the Hospice and Palliative Care Unit because they experienced a natural course of death and received the least medical intervention. Despite the pulse of the cancer patients being recorded only once daily, similar results to the rat study confirmed that the HCVs could be used as a quantitative indicator reflecting physiological changes during the dying process. This result is also consistent with the statement of Singh *et al.*, 'the (single or 1-min or even 24-h) measurement of heart rate and blood pressure can be taken to ascertain whether a patient is dead or alive [24]'.

In clinical practice, systolic and diastolic blood pressures are important physiological indicators, and a dramatic drop in blood pressure is viewed as an important danger sign. However, due to treatment interventions, these indicators are usually kept within normal range [11]. The systolic and diastolic blood pressures on the last day of the patients were not significantly different from that of the second to last day, but we found that the mean systolic blood pressure was higher on the last day (Table 1), an example of treatment keeping the blood pressure within normal range. In addition, only two of the patients that expired during our study had systolic blood pressure below 90 mmHg and diastolic blood pressure below 60 mmHg on the last day when we recorded the data; the other six patients that expired had blood pressures that were within normal range. The recorded HCVs, however, reflected the dying process by losing stability in all harmonic components. Although one study has shown that the pulse rate variability is not a surrogate for heart rate variability [33], HCVs might reveal more cardiovascular information in dying patients.

Furthermore, when comparing all groups, the HCVs of the expired patients increased gradually first in the high-frequency components and then in the low-frequency components. We conclude that the HCVs reflect the dying process in a quantitative way and clearly indicate the severity of illness for both humans and rats. It is possible that beat-to-beat fluctuations in the Fourier components of the cardiovascular rhythm could provide us with a measure of the body's health.

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References

1 Glass L. Synchronization and rhythmic processes in physiology. *Nature* 2001; **410**:277–284.
2 Cull DJ, Chernow B. Predicting outcome in critically ill patients. *Crit Care Med* 1994; **22**:1345–1369.
3 Hardy JR, Turner R, Saunders M, Herny R. Prediction of survival in a hospital-based continuing care unit. *Eur J Cancer* 1994; **30A**:284–288.
4 Morita T, Ichiki T, Tsunoda J, Inoue S, Chihara S. A prospective study on the dying process in terminally ill cancer patients. *Am J Hospice Palliative Care* 1998; **15**:217–222.
5 Maltoni M, Pirovano M, Scarpi E, Marinari M, Indelli M, Amoldi E, *et al.* Prediction of survival of patients terminally ill with cancer: results of an Italian prospective multicentric study. *Cancer* 1995; **75**:2613–2622.
6 Morita T, Tsunoda J, Inoue S, Chihara S. Survival prediction of ill cancer patients by clinical symptoms: development of a simple indicator. *Jpn J Clin Oncol* 1999; **29**:156–159.
7 Moreno R, Apolone G, Miranda DR. Evaluation of uniformity of fit of general outcome prediction models. *Intensive Care Med* 1998; **24**:40–47.
8 Morita T, Tsunoda J, Inoue S, Chihara S. Palliative prognostic index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer* 1999; **7**:128–133.
9 Pierpont GL, Parenti CM. Physician risk assessment and APACHE scores in cardiac care units. *Clin Cardiol* 1999; **22**:366–368.
10 Hunter A, Kennedy L, Henry J, Ferguson I. Application of neural networks and sensitivity analysis to improved prediction of trauma survival. *Comput Methods Programs Biomed* 2000; **62**:11–19.
11 Tan IK. APACHE and SAPS are poorly calibrated in Hong Kong intensive care units. *Ann Acad Med Singapore* 1998; **27**:318–322.
12 Yien HW, Hseu SS, Lee LC, Kuo TB, Lee TY, Chan SH. Spectral analysis of systemic arterial pressure and heart rate signal as a prognostic tool for the prediction of patient outcome in the intensive care unit. *Crit Care Med* 1997; **25**:258–266.
13 Cerutti C, Barres C, Paultre C. Baroreflex modulation of blood pressure and heart rate variability in rats: assessment by spectral analysis. *Am J Physiol* 1994; **266**:H1993–H2000.
14 Plamen C, Luis A, Ary L, Michael G, Zbigniew R, Eugene H. Multifractality in human heart rate dynamics. *Nature* 1999; **399**:461–465.
15 Huikuri HV, Makikallio T, Airaksinen KE, Mitrani R, Castellanos A, Myerburg RJ. Measurement of heart rate variability: a clinical tool or a research toy? *J Am Coll Cardiol* 1999; **34**:1879–1883.
16 Dankner R, Goldbourt U, Boyko V, Reicher-Reiss H. Predictors of cardiac and non-cardiac mortality among 14,697 patients with coronary heart disease. *Am J Cardiol* 2003; **91**:121–127.
17 Conci F, Rienzo MD, Castiflioni P. Blood pressure and heart rate variability and baroreflex sensitivity before and after brain death. *J Neurol Neurosur Psychiatry* 2001; **71**:621–631.
18 Makikallio TH, Huikuri HV, Makikallio A, Sourander LB, Mitrani R, Castellanos A, *et al.* Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. *J Am Coll Cardiol* 2001; **37**: 1395–1402.
19 Forslund L, Bjorkander I, Ericson M, Held C, Kahan T, Rehnqvist N, *et al.* Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. *Heart* 2002; **87**:415–422.
20 Bilchick KC, Fetics B, Djoukeng D, Fisher SG, Fletcher RD, Singh SN, *et al.* Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs Survival Trial of Anti-arrhyghmic Therapy in Congestive Heart Failure). *Am J Cardiol* 2002; **90**:24–28.
21 Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, *et al.* Low heart rate variability in a two-minute rhythm strip predicts of coronary heart disease and mortality form several causes. *Circulation* 2002; **102**:1239–1244.
22 Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability form short electrocardiographic recordings predicts mortality form all causes in middle-aged elderly men. *Am J Epidemiol* 1997; **145**:899–908.
23 Poon CS, Christopger KM. Decrease of cardiac chaos in congestive heart failure. *Nature* 1997; **389**:2492–2495.
24 Huikuri HV, Makikallio TH, Airaksinen KE, Seppanen T, Puukka P, Raiha IJ, *et al.* Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Am Heart Assoc* 1998; **97**:2031–2036.
25 Singh RB, Cornelissen G, Weydahl A, Schwartzkopff O, Katinas G, Otsuka K, *et al.* Circadian heart rate and blood pressure variability considered for research and patient care. *Int J Cardiol* 2003; **87**:9–28.
26 Mahomed FA. The physiology and clinical use of the sphygmograph. *Med Times Gazette* 1972; **1**:62.
27 O'Rourke MF, Pauca A, Jiang XJ. Pulse wave analysis. *Br J Clin Pharmacol* 2001; **51**:507–522.
28 Kuo YC, Wang WK. Harmonic variations of arterial pulse during dying process of rats. *Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (2001).
29 Wang WK, Chen HL, Hsu TL, Wang Lin YY. Alteration of pulse in human subjects by three Chinese herbs. *Am J Chin Med* 1994; **12**: 197–203.
30 Wang Lin YY, Chang SL, Win YE, Hsu TL, Wang WK. Resonance–the missing phenomenon in haemodynamics. *Circ Res* 1991; **69**: 246–249.
31 Yu GL, Wang Lin YY, Wang WK. Resonance in the kidney system of rats. *Am J Physiol* 1994; **267**:H1544–H1548.
32 Wang WK, Hsu TL, Wang Lin YY. Liu-Wei-Dihuang: a study by pulse analysis. *Am J Chin Med* 1997; **16**:73–82.
33 Constant I, Laude D, Murat I, Elghozi JL. Pulse rate variability is not a surrogate for heart rate variability. *Clin Sci* 1999; **97**:391–397.