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Raising Harmonic Variation of Arterial Pulse in Dying Rats

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Abstract: Our previous study revealed that the coefficient of variation of harmonic magnitude (HCV) of radial arterial pulse was significantly raised before the death of cancer patients. In this study, we recorded the caudate arterial pulse of 24 Sprague-Dawley rats that had a fatal dose of urethane injected into their abdomens. Twenty rats were dead within 3 hours after the injection and four survived. We defined the last 100 minutes of each rat's life as the dying process. During the dying process, we found that both the systolic blood pressure and diastolic blood pressure dropped steeply during the last 5 minutes. However, all HCVs, except HCV1, climbed steeply before the last 5 minutes. The HCV1 of the dying rats was significantly higher than that of rats that survived, starting from the first minute ($P < 0.01$). The HCV2 of the dying rats was significantly higher than that of the survived rats starting from the 52nd minute ($P < 0.05$). The HCV3 and HCV4 of the dying rats were significantly higher than those of the survived rats until the 70th minute and the 80th minute, respectively ($P < 0.05$). Furthermore, HCV2–HCV4 proceeded with the dying process and increased gradually. We concluded that HCVs, which failed first in the high-frequency components and then in the low-frequency components, could provide physicians with earlier information to prevent the coming failure of circulatory system, and could reflect quantitatively pathological severity and predict patient outcome. The specific Fourier components in the pulse provide more physiological information than systolic and diastolic blood pressures.

Keywords: Arterial Pulse; Dying Process; Harmonic Coefficient of Variation.

Correspondence to: Dr. Yuh-Ying Lin Wang, Biophysic Laboratory, Institute of Physics, Academia Sinica, Nankang, Taipei, Taiwan 11529. Tel: (+886) 2-2788-0058 (ext. 2050), Fax: (+886) 2-2783-4187, E-mail: wkwang@phys.sinica.edu.tw

Introduction

Physicians who practice traditional Chinese medicine use the pulse to diagnose disease, evaluate patients' physical conditions, and even predict death. These issues have been discussed in Chinese medicine. For example, as stated in the Chinese medicine "bible," *Huang-Ti-Nei-Ching*, "Differential diagnosis of the *Yang Chi* in pulse can detect the time factors which influence on diseases. Differential diagnosis of the *Yin Chi* in pulse can predict the death of patients. When the *hepatic Chi* in pulse fails, the man will die in 18 days. When the *renal Chi* in pulse fails, the man will die in seven days. When the *cardiac Chi* in pulse fails, the man will die in nine days. When the *pulmonary Chi* in pulse fails, the man will die in 12 days. When the *spleenic Chi* in pulse fails, the man will die in four days." (*Huang-Ti-Nei-Ching*, 1981a and b) The importance of the information within arterial pulse waves has been recognized in clinical medicine for a long time (Mahomed, 1872). 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 the treatment interventions, these indicators are usually kept within normal range (Tan, 1998). Thus, the advanced analysis of blood pressure has become a new direction of research (Yien *et al*., 1997). Arterial pulse wave analysis has been employed widely in clinical practice, such as in hypertension, cardiac failure and aging (O'Rourke *et al*., 2001). However, the scientific meaning of "*hepatic*, *renal* or *spleenic Chi* in pulse fails" remains unclear. Is there any quantitative indicator in pulse available to evaluate patients' physical condition? Can it process with the dying process? Do the specific components in pulse represent more physiological information than just the systolic and diastolic blood pressure? These questions are interesting and valuable for both Chinese medicine and scientific medicine.

In previous study, we found that each organ and its related meridian are in resonance with a specific Fourier component of pressure wave (Wang Lin *et al*., 1991; Wang *et al*., 1996). We also suggested that the lower frequency components were referred to as "*Yin*" and the higher ones as "*Yang*" (Wang *et al*., 1997). Recently, we found that the coefficient of variations of harmonic magnitudes (HCVs) of radical arterial pulse increased significantly before death in patients with cancer (Kuo *et al*., 2002). According to our physical model simulation and clinical investigation, the raised variation might be due to the increase of arteriolar openings responded to local ischemia. Because coefficient of variations account for the variability, it seems that Fourier components of pressure wave lose stability before the death. As stated in *Huang-Ti-Nei-Ching*, "the pathological factor *feng* (風), tend to shift the location and vary." Thus, the HCVs may be related to the "*feng*" in Chinese medicine. We hypothesized that HCVs could be pathological indicators to the dying process. If it is true, HCVs could be used to evaluate physical condition and predict the patients' outcome or death. This study was conducted on dying process of rats to confirm the proposal and try to figure out the scientific meaning for the failure of *hepatic*, *renal* or *spleenic Chi* in pulse.

Methods

Twenty-four Sprague-Dawley rats weighing 300 to 350 g were anesthetized with urethane (1.2 mg/g body weight). The caudate arteries were cannulated via a $\frac{3}{4}$-inch (25G) intravenous catheter. Blood pressure signals were recorded using a P10 EZ pressure gauge. The system's tested level frequency response could reach 60 Hz, and the signal, after amplification through a Gould amplifier and processing through an A-D converter with sampling rate of 500 data points/second, was entered into an IBM PC for analysis. The pulse spectrum was analyzed with a Fourier transformation that used T (period) = 1 pulse time (Yu *et al*., 1994).

After each rat was anesthetized, pulse measurements were taken every minute. After Fourier transformation, we analyzed the first six harmonic magnitudes. Each measurement contained 7–10 pulses. The mean value of the magnitude and standard deviation of each harmonic were calculated. The coefficient of variation equals the standard variation divided by the mean (Kuo *et al*., 2002).

After the blood pressure had stabilized for 30 minutes, the fatal dose of urethane was injected into the rats' I.P. Twenty rats were dead within 3 hours after injection, and we defined the last 100 minutes of each rat's life as the dying process. The other four rats survived and were used as the control group. The mean values of the systolic blood pressure, diastolic blood pressure, and the individual harmonic components were also calculated as near-death data.

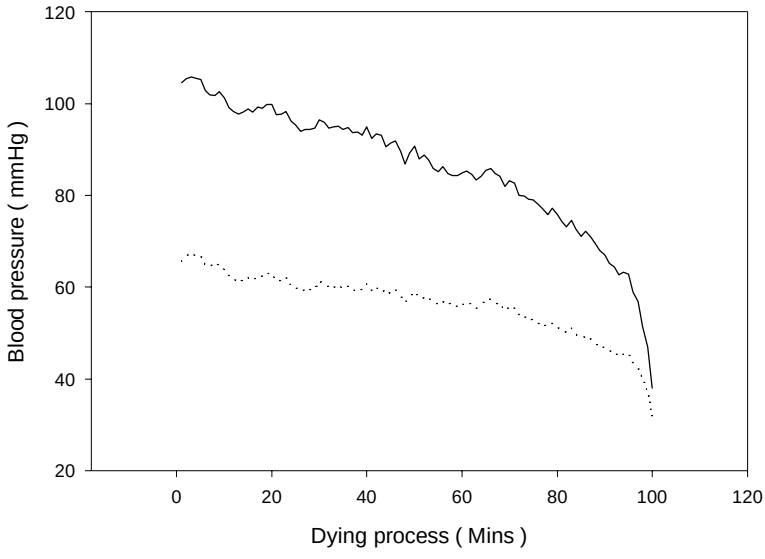
Results

The systolic and diastolic blood pressures of the rats during the dying process were plotted and are shown in Fig. 1A. The systolic blood pressure decreased gradually, from 104.5 ± 5.3 to 38.6 ± 4.3 mmHg (mean ± SE). The diastolic blood pressure decreased slightly, from 65.6 ± 3.4 to 55.3 ± 3.5 mmHg during the first 70 minutes; then fell to 31.8 ± 3.6 mmHg during the last 30 minutes. Both the systolic and diastolic blood pressures dropped steeply during the final 5 minutes. In clinical practice, this dramatic drop in blood pressure indicates failure of the circulatory system.

The systolic and diastolic blood pressures of all rats were plotted and are shown in Fig. 1B. The mean systolic and diastolic blood pressures of the survived rats were 93.1 ± 0.3 and 60.7 ± 0.3 mmHg, respectively. After t tests were done, we found that the systolic blood pressure of the dying rats was significantly lower than that of the survived rats after the 54th minute, and the diastolic blood pressure of the dying rats was significantly lower than that of the survived rats until the 69th minute.

The HCV1 of the rats during the dying process was plotted and is shown in Fig. 2A. During the dying process, HCV1 increased from 2.3 ± 0.3% to 5.5 ± 1.4%. In the final 5 minutes, the HCV1 rose steeply. The HCV1 of all rats was plotted and is shown in Fig. 2B. The mean HCV1 of the survived rats was 1.7 ± 0.0%. After t tests were done, we found that the HCV1 of the dying rats was significantly higher than that of the survived rats, starting from the first minute. HCV1 clearly distinguished the dying process from the near-dying process. HCV1 could be a pathological indicator to forecast death.

(A)



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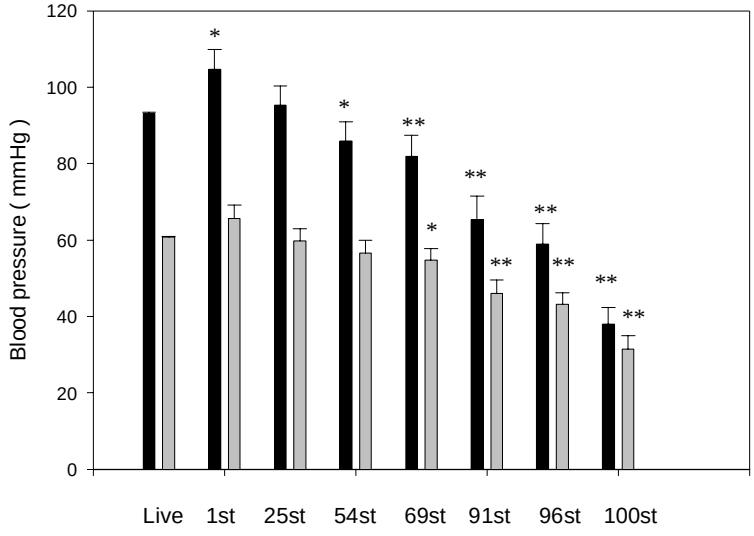


Figure 1. (A) Mean blood pressure of dead rats (n = 20) during the dying process. The solid line represents systolic blood pressure, and the dotted line represents diastolic blood pressure. (B) Blood pressure of the survived rats (n = 4) compared with those died (n = 20). Values are means ± SE. X (horizontal) axis represents different groups (Groups 1 through 8). Group 1 was composed of survived rats (1428 measurements taken). Groups 2 through 8 were composed of dead rats (20 measurements taken each). The numbers represent the time their systolic and diastolic blood pressures were measured. Y (vertical) axis represents blood pressure (mmHg). The black bars represent systolic blood pressure and the gray bars represent diastolic blood pressure. $^{*}P < 0.05$ versus survived rats, $^{**}P < 0.01$ versus survived rats (Groups 1).

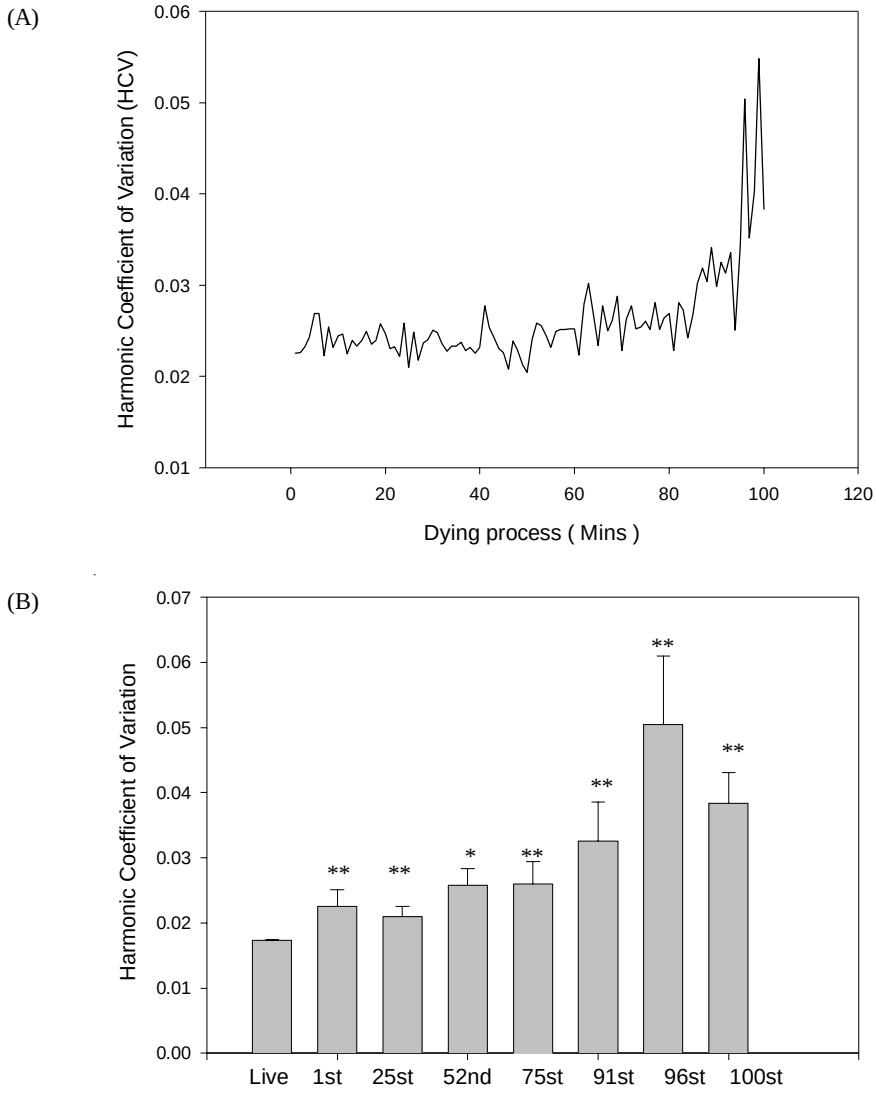


Figure 2. (A) Mean coefficient of variation of the first harmonic component (HCV1) of dead rats (n = 20) during the dying process. X (horizontal) axis represents time (minutes) and Y (vertical) axis represents coefficient of variation of harmonic magnitude (HCV). (B) Coefficient of variation of the HCV1 of rats that survived (n = 4) and those died (n = 20). Values are means ± SE. X (horizontal) axis represents different groups (Bars 1 through 8) and Y (vertical) axis represents coefficient of variation of harmonic magnitude (HCV). Bar 1 shows the mean HCV1 of survived rats (1428 measurements taken). Bars 2 through 8 show the HCV1 of dead rats, taken at the indicated time (20 measurements taken each). $^{*}P < 0.05$ versus rats that survived, $^{**}P < 0.01$ versus survived rats (Bars 1).

The HCV2 of rats during the dying process was plotted and is shown in Fig. 3A. During the dying process, HCV2 increased gradually, from 4.6 ± 0.5% to 10.4 ± 2.4% during the first 87 minutes, and then climbed steeply to 14.2% during the last 13 minutes. The HCV2 of all rats was plotted and is shown in Fig. 3B. The mean HCV2 of the survived rats was 5.2 ± 0.1%. After t tests were done, we found that the HCV2 of the dying rats was significantly higher than that of the survived rats, starting from the 52nd minute. Systolic blood pressure, diastolic blood pressure and the HCV2 all showed clear decreasing or increasing trends during the dying process. However, HCV2 was an earlier indicator that distinguished the dying process from the near-dying process. HCV2 could be a good pathological indicator to indicate the dying process and evaluate physical condition.

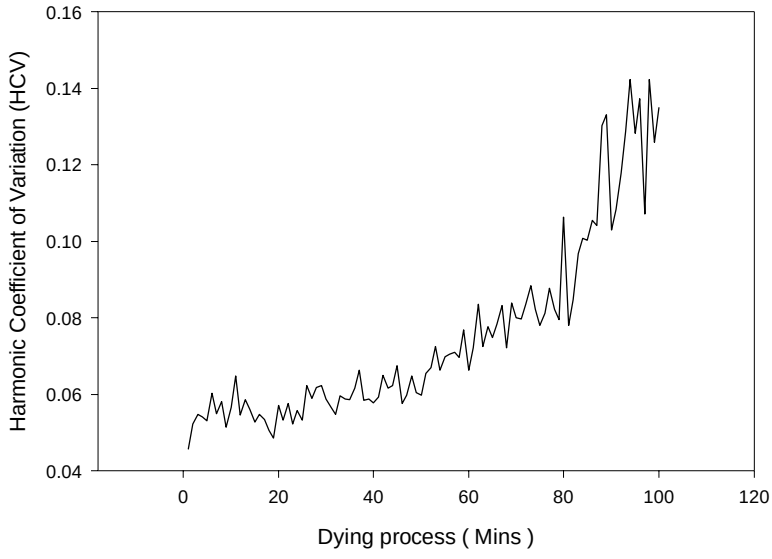
The HCV3 of rats during the dying process was plotted and is shown in Fig. 4A. HCV3 showed a clear increasing trend. It rose gradually from 17.5 ± 0.3% to 30.5 ± 5.5% during the first 85 minutes, then climbed steeply to 52.9 ± 9.9% in the last 15 minutes. The HCV3 of all rats was plotted and is shown in Fig. 4B. The HCV3 of survived rats was 19.8 ± 0.5%. After t tests were done, we found that the HCV3 of the dying rats was significantly higher than that of the survived rats until the 70th minute.

The HCV4 of the rats during the dying process were plotted and shown in Fig. 5A. During the dying process, the HCV4 had a clear increasing trend. It rose gradually from 48.6 ± 8.8% to 94.4 ± 14.8% in the first 82 minutes, then climbing steeply to 223.6 ± 92.3% and with great fluctuations in the last 18 minutes. The HCV4 of all rats was plotted and is shown in Fig. 5B. The HCV4 of survived rats was 60.8 ± 1.4%. After t tests were done, we found that the HCV4 of the dying rats was significantly higher than that of the survived rats until the 80th minute.

The HCV5 of rats during the dying process was plotted and is shown in Fig. 6A. HCV5 was near 100% at the beginning and showed no clear increasing trend during the first 75 minutes of the dying process, when compared to the survived rats. However, it increased steeply to 1051.5 ± 539.9% during the last 20 minutes. The HCV5 of all rats was plotted and is shown in Fig. 6B. The HCV5 of the survived rats was 235.0 ± 7.6%. After t tests were done, we found that the HCV5 of the dying rats were significantly lower than that of the survived before the 53rd minute. Between the 54th and 87th minutes, there was no significant difference between the dying and survived rats. After the 88th minute, the HCV5 of the dying rats was significantly higher than that of the survived rats, except at the 96th, 97th and 99th minutes.

The HCV6 of rats during the dying process was plotted and is shown in Fig. 7A. During the dying process, HCV6 was more than 190% in the beginning and showed no clear increasing trend before first 76 minutes of the dying process, when compared to the survived. However, it increased sharply to 2198.9 ± 754.9% during the last 24 minutes. The HCV6 of all rats was plotted and is shown in Fig. 7B. The HCV6 of the rats that survived was 596.2 ± 37.4%. After t tests were done, we found that the HCV6 of the dying rats was significantly higher than that of the survived rats only during the 91st, 92nd, 94th and 100th minutes. Except for these 4 minutes, there was no significant difference between these two groups.

(A)



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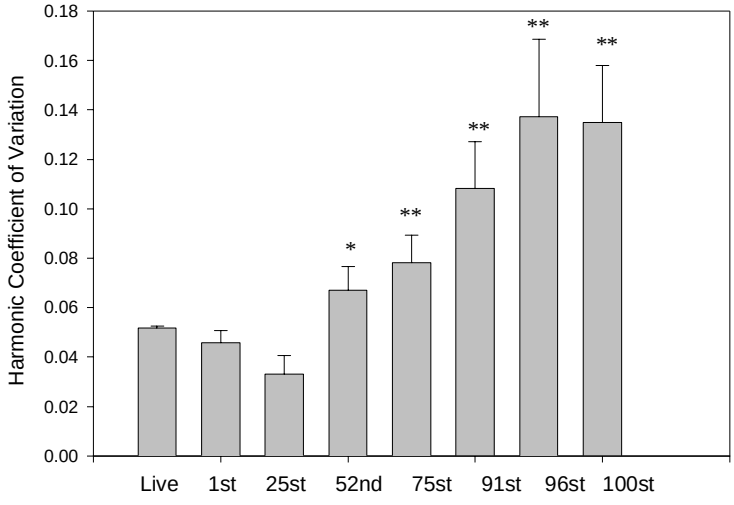
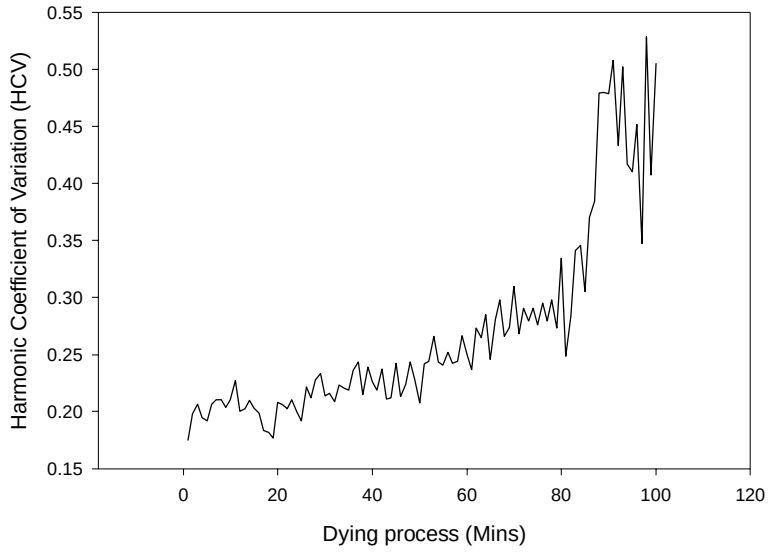


Figure 3. (A) Mean coefficient of variation of the second harmonic component (HCV2) of dead rats (n = 20) during the dying process. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. (B) Coefficient of variation of the HCV2 of the survived rats (n = 4) and those died (n = 20). Values are means ± SE. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. $^{*}P < 0.05$ versus rats that survived, $^{**}P < 0.01$ versus rats that survived (Bars 1).

(A)



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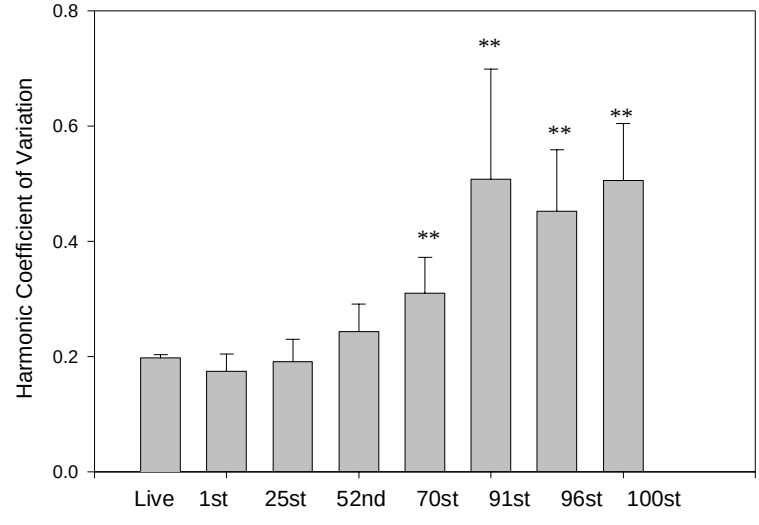


Figure 4. (A) Mean coefficient of variation of the third harmonic component (HCV3) of dead rats (n = 20) during the dying process. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. (B) Coefficient of variation of the HCV3 of survived rats (n = 4) and those died (n = 20). Values are means ± SE. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. $^{*}P < 0.05$ versus rats that survived, $^{**}P < 0.01$ versus rats that survived (Bars 1).

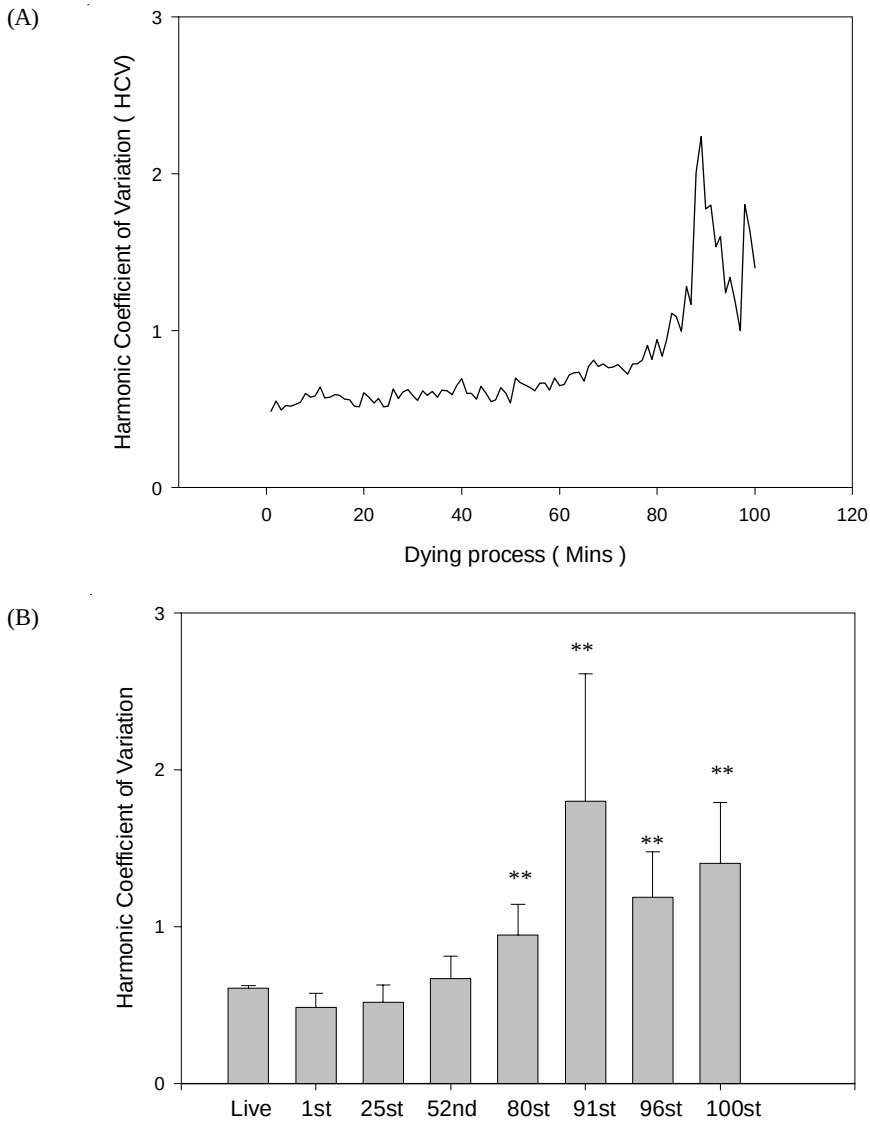
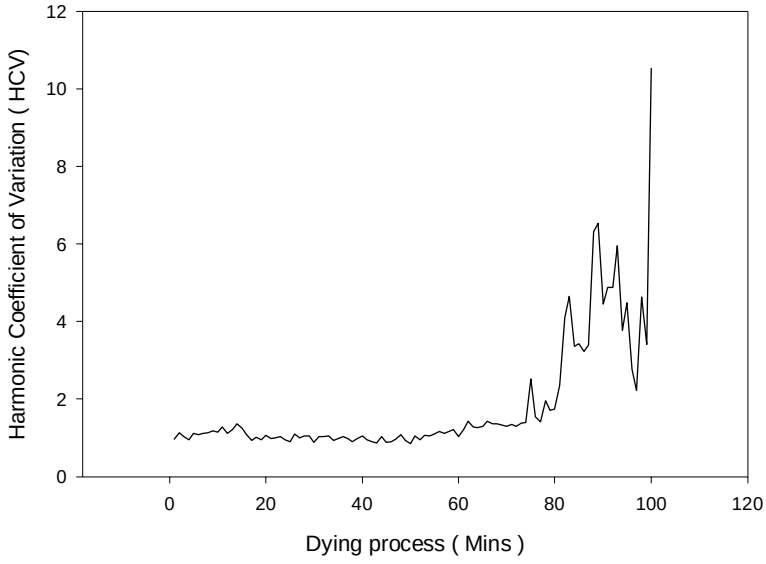


Figure 5. (A) Mean coefficient of variation of the fourth harmonic component (HCV4) of dead rats (n = 20) during the dying process. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. (B) Coefficient of variation of the HCV4 of rats that survived (n = 4) and those died (n = 20). Values are means ± SE. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. $^{*}P < 0.05$ versus rats that survived, $^{**}P < 0.01$ versus rats that survived (Bars 1).

(A)



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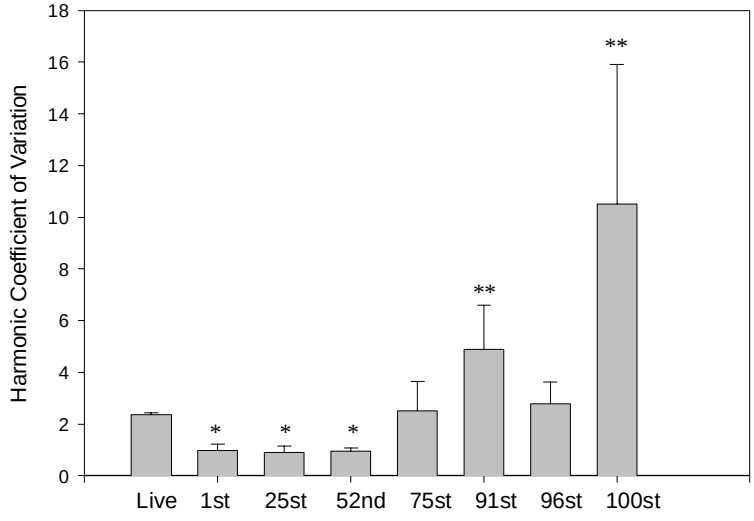

Figure 6. (A) Mean coefficient of variation of the fifth harmonic component (HCV5) of dead rats (n = 20) during the dying process. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. (B) Coefficient of variation of the HCV5 of the rats that survived (n = 4) and those that died (n = 20). Values are means ± SE. Values are means ± SE. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. $^{*}P < 0.05$ versus rats that survived, $^{**}P < 0.01$ versus rats that survived (Bars 1).

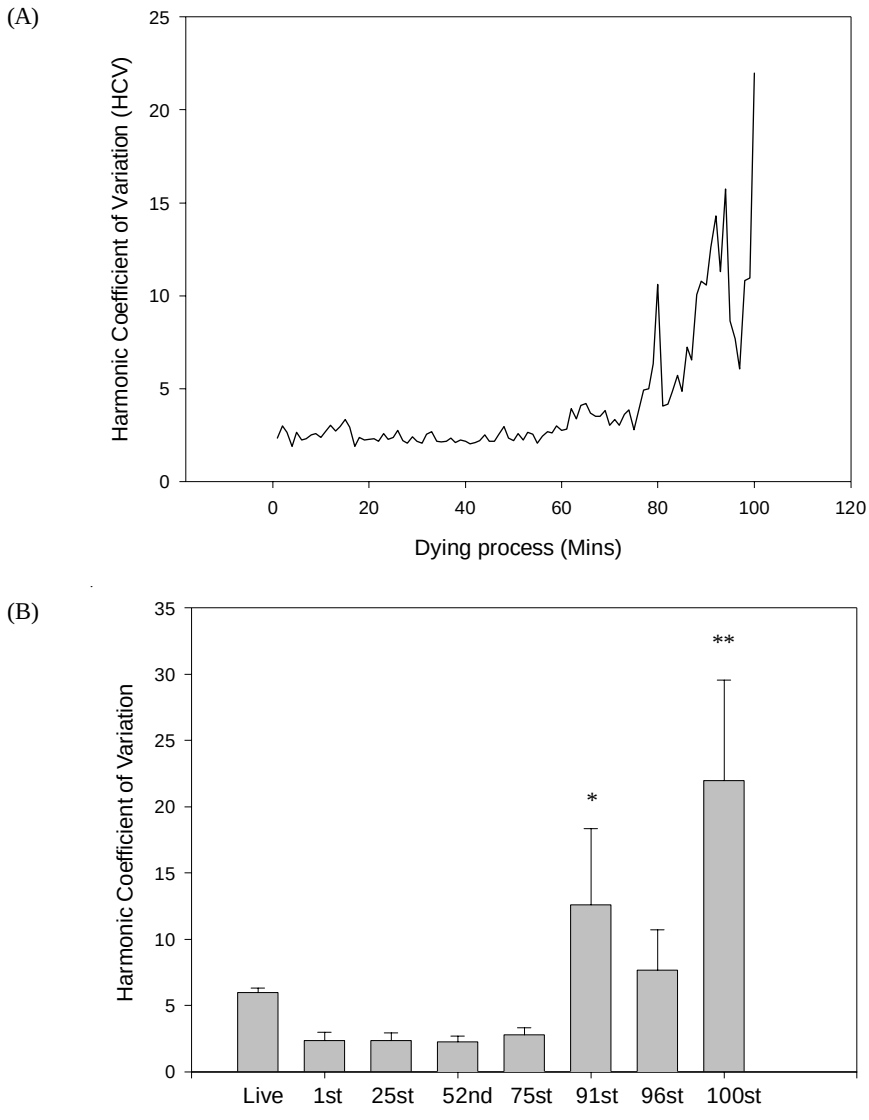

Figure 7. (A) Mean coefficient of variation of the sixth harmonic component (HCV6) of dead rats (n = 20) during the dying process. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. (B) Coefficient of variation of the HCV6 of the rats that survived (n = 4) and those that died (n = 20). Values are means ± SE. Values are means ± SE. X (horizontal) axis and Y (vertical) axis represent the same as described in Fig. 2. $^{*}P < 0.05$ versus rats that survived, $^{**}P < 0.01$ versus rats that survived (Bars 1).

Discussion

The rats' HCVs increased during the dying process, which is also seen in patients with end-stage cancer. Furthermore, HCV2–HCV4 increased gradually as the dying process progressed. This confirms that the HCVs could be used as quantitative indicators of physiological changes during the dying process. This result also agrees with the statement of Singh *et al*. (2003) "the (single or 1 minute or even 24 hours) measurement of heart rate and blood pressure can be taken to ascertain whether a patient is dead or alive."

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 of the failure of the circulatory system. However, the drop in diastolic or systolic blood pressure always comes suddenly. This danger sign does not provide enough time for physicians to prevent the coming of circulatory failure. In this study, we also found that both the systolic and diastolic blood pressures dropped steeply during the last 5 minutes, while during the same time, HCV1 was climbing steeply. Because the first harmonic is the fundamental frequency of blood pressure pulse, we suggest that the climbing HCV1 is an indicator of blood pressure failure and is related to the failure of the circulatory system.

The other five HCVs climbed steeply before the last 5 minutes of life. HCV2 climbed during the last 13 minutes, HCV3 during the last 15 minutes, HCV4 during the last 18 minutes, HCV5 during the last 20 minutes and HCV6 during the last 24 minutes. If the climbing of the HCVs indicates the significant fluctuation and failure of these components, this indicates that the Fourier components of blood pressure wave fail individually from higher components to the lower ones before the drop in diastolic or systolic blood pressure. Therefore, HCVs could provide earlier information for physicians to predict patient outcome and prevent final collapse. In addition, the HCVs, which account for variability and shift in different harmonic components, are related to the pathological factor "*Feng*" in Chinese medicine. Furthermore, internal "*hepatic feng*" indicates the worst condition and is related to the failure of the circulatory system.

In a previous study, we suggested that the lower frequency components were referred to as "*Yin*" and the higher ones as "*Yang*" (Wang *et al*., 1997). The results of the present study show that the HCV1 of dying rats was significantly different from that of survived and that HCV2–HCV4 increased during the dying process. However, the HCV5 and HCV6 of dying rats did not show any significant differences from those of the survived. These data agree with the statement in the *Huang-Ti-Nei-Ching*, "Differential diagnosis of the *Yin Chi* in pulse can predict the death of patients." Meanwhile, the *hepatic*, *renal*, *spleenic*, and *pulmonary Chi* in pulse being related to the lower Fourier components of the pressure wave has already been proven before (Wang *et al*., 1995). Although the exact time frame of the specific Fourier components of the pulse requires further study, our results provide physicians with new ways to inspect the blood pressure. The specific Fourier components of the pulse provide more physiological information than systolic and diastolic blood pressures, and the HCVs can be used as pathological indicators.

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