31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

A survival prediction model of hemorrhagic shock in rats using a logistic regression equation.

Tak Hyung Lee, Ju Hyung Lee, Sang Won Chung, Hyung Wook Noh, Young Woo Shim and Deok Won Kim

Abstract— **Hemorrhagic shock is a common cause of death in emergency rooms. Since the symptoms of hemorrhagic shock occur after shock has considerably progressed, it is difficult to diagnose shock early. The purpose of this study was to improve early diagnosis of hemorrhagic shock using a survival prediction model in rats. We measured ECG, blood pressure, respiration and temperature in 45 Sprague-Dawley rats, and then obtained a logistic regression equation predicting survival rates. Area under the ROC curves was 0.99. The Hosmer-Lemeshow goodness-of-fit chi-square was 0.86 (degree of freedom=8, p=0.999). Applying the determined optimal boundary value of 0.25, the accuracy of survival prediction was 94.7%.**

I. Introduction

In 1990, about five million people died worldwide as a result of injury [1]. For people younger than 35 years, injury is now a leading cause of death. Nevertheless, the global epidemic of injury is only beginning. By 2020, deaths from injury will probably increase to eight million [2]. About one-third of these deaths will result from hemorrhagic shock [3]. In South Korea, it was reported that the cause of 74% of multiple trauma patients' death in an emergency room (ER) in the past eight years was due to hypovolemic shock [4].

Hemorrhagic shock is a clinical syndrome characterized by widespread inadequate oxygenation and supply of nutrients to tissues and organs, resulting in cellular dysfunction [5], [6]. This imbalance is the most fundamental problem in all types of shock. If shock occurs, it is not difficult to diagnose because the clinical symptoms are quite clear but if organ function changes abnormally and irreversibly, the effectiveness of treatment would be poor. However, diagnosis and treatment could be delayed for the early stages of shock as there are no obvious symptoms. Therefore, the importance of evaluation for the early stages of shock and treatment should be emphasized [7], [8]. Most shock models comprehensively measured and analyzed biosignals such as ECG, blood pressure, respiration and temperature, which were standard indicators of hemorrhagic shock. These models are highly needed but they have not been successfully carried out until now. Even though several real-time online systems have been reported, most of them analyzed the frequency of ECG variation and heart rate variability (HRV) or blood pressure variability.

In this study, we constructed an integrated system to control bleeding and simultaneously measure biosignals such as ECG, blood pressure, temperature and respiration for monitoring physiological characteristics, and making a prognosis of hemorrhagic shock according to stage.

II. Materials and Methods

A. Animal preparation

Forty-five male Sprague-Dawley (S-D) rats, eight to nine weeks old, weighing 300 to 360 g, were used in the study. The rats were anesthetized using Zoletil 50 (0.21 ml/300 g, Virbac, France) and placed in the supine position on an operating table. After we incised both inguinal areas, a catheter (24 gauge, Becton Dickinson Korea, Korea) was inserted into the right femoral artery to measure arterial blood pressure and another catheter (22 gauge) was inserted into the left femoral vein to draw blood as shown in Fig. 1. All experimental procedures and protocols of this study were approved by the Institutional Animal Care and Use Committee of Yonsei University Health System, Seoul, Korea.

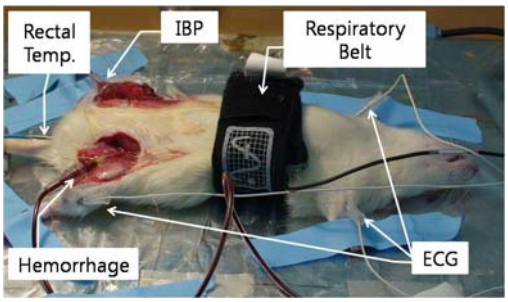

Fig. 1. Photo of experimental setup for hemorrhagic shock

This work was supported in part by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea Government (MEST) (No. R01-2007-000-20819-0)

T. H. Lee is with the Graduate Program in Biomedical Engineering, Yonsei University, Seoul, Korea (E-mail: picf@yuhs.ac).

J. H. Lee is with the Graduate Program in Biomedical Engineering, Yonsei University, Seoul, Korea (E-mail: ssziq33@yuhs.ac).

S. W. Jung is with the Dept. of Emergency Medicine, College of Medicine, Kwandong University, Koyang, Korea (E-mail: gemini61@hitel.net).

H. W. Noh is with the Graduate Program in Biomedical Engineering, Yonsei University, Seoul, Korea (E-mail: happy05@yuhs.ac).

Y. W. Shim is with the Brain Korea 21 Project for Medical Science, Yonsei University, Seoul, Korea (E-mail: tladuddn@yuhs.ac).

D. W. Kim is a Professor at the Dept. of Medical Engineering, College of Medicine, Yonsei University, Seoul, Korea (E-mail: kdw@yuhs.ac).

B. Measurement system

We measured analog signals such as ECG, arterial blood pressure, respiration, and temperature with the sampling frequency of 1 kHz using LabChart 6 Pro (AD Instruments, USA) as explained in detail below. Fig. 2 and 3 show the block diagram of the measurement system and obtained raw signals, respectively.

1) ECG: After ECG signals were acquired using invasive needle electrodes and amplified by Animal Bio Amp (ML136, AD Instruments, USA), they fed into the A/D system (PowerLab 8/30, AD Instruments).

2) Arterial pressure: Invasive blood pressure (IBP) amplifier was constructed using an instrumentation amplifier (AD620, Analog Device, USA) and a piezo-resistive silicon pressure sensor (1620 Pressure Sensor, MSI Sensors, USA) that was calibrated with a mercury sphygmomanometer.

3) Respiration: Respiration was obtained by measuring changes in the thoracic cross-sectional area using a respiratory belt (AD Instruments).

4) Temperature: We measured the rats' temperatures using a rectal probe (MLT1403, AD Instruments, USA). It was inserted into the rectum approximately 5 cm deep.

5) Hemorrhagic controller: We utilized a withdrawal syringe pump (Pump 11 Plus, Harvard Apparatus, USA) for quantitatively controlled bleeding.

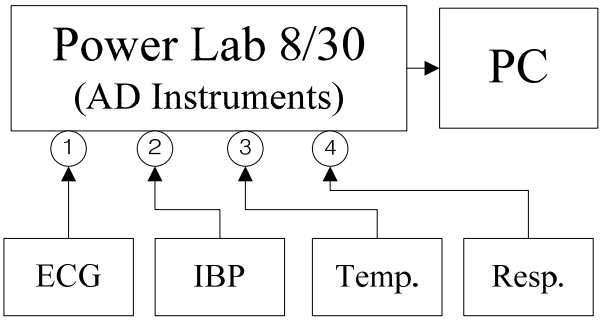

Fig. 2. Block diagram of the measurement system

Fig. 3. Chart Pro real- time analysis on screen

C. Protocol

Room temperature was between 20.5 to 23.5°C and humidity was between 40 to 60% during experiments. Body temperature was maintained at 36.5 to 37.5°C using a heating pad during resting periods.

Rats rested for 15 min before the experiments as shown in Fig. 4. Three blood volumes of 2 ml/100 g, 2.5 ml/100 g and 3 ml/100 g were withdrawn for three groups. Each group was composed of 15 animals. The duration of blood withdrawal was 15 min. Hemorrhagic shock was induced by withdrawing blood from a femoral vein, and all data measured by the integrated system were collected until death or at 150 min from the beginning of resting. If the rats lived up to 150 min, they were given a merciful death. Death was defined as when there was no mean arterial pressure (MAP) [9].

D. Data analysis

We analyzed data of the 5 min before and after "Bleeding

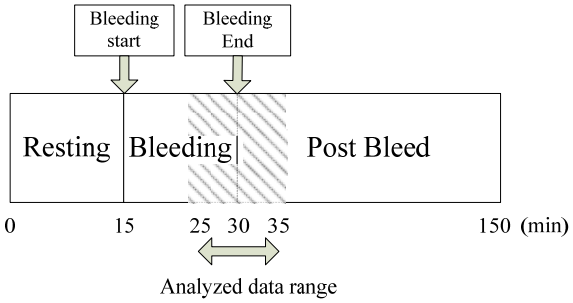

Fig. 4. Experimental protocol

end" (the shaded area) in Fig. 4. We selected this period because we simulated the emergency situation in which bleeding patients arrive and then they are treated for no bleeding in ER. HR from ECG, systolic blood pressure (SBP) and MAP from measured blood pressure waves, respiration rates and temperature were the parameters chosen for analysis. Data of 10 min for each parameter for each rat were divided into 10 sets of data with one-min averages. Using this method, 450 data sets were made.

For the multiple logistic regression analysis, 300 data sets were used to determine a logistic regression equation and the other 150 data sets were used to test the obtained equation. Statistical software SPSS 12.0 (SPSS Inc, USA) was used for obtain the equation. Forward selection method was used to select the variables for the logistic regression equation. The survival group was represented as a value of 1and the death group was represented as 0. Output of the logistic regression equation predicts survival rates between 0 and 1.

The discriminatory power of the logistic regression was analyzed using the area under the receiver operating characteristic (ROC) curves. An area under the ROC curve of 1.0 implies perfect discrimination, whereas an area under the ROC curve of 0.5 is equivalent to a random model. Calibration of the model was measured by computation of the

Hosmer-Lemeshow goodness-of-fit chi-square statistic (HL statistics) [10]. The smaller the HL statistics, the better the fit, with a perfectly calibrated model having a value of zero [11].

III. Result

Among the 45 rats, all 15 rats from the 2 ml group and four rats from the 2.5 ml group survived until two hours after bleeding end from blood loss, while all 15 rats from the 3 ml group and 11 rats from the 2.5 ml group died. As shown in Table I, all measured data were expressed as mean ± standard error for each experimental group between 25 and 35minutes of the experiment. The 2.5 ml group was divided into death and survival groups.

TABLE I
THE MEAN ± STANDARD ERROR FOR ANALYZED RANGE DATA

Group	HR (BPM)	SBP (mmHg)	MAP (mmHg)	Resp (BPM)	Temp (°C)
2ml	220.34	67.46	39.95	175.99	35.02
(Alive; n=15)	±5.78	±1.30	±0.89	±3.07	±0.06
2.5ml	183.94	55.70	33.73	165.48	35.23
(Alive; n=4)	±5.29	±1.28	±0.88	±5.75	±0.08
2.5ml	303.28	39.90	24.55	115.70	34.92
(Dead; n=11)	±7.65	±0.67	±0.28	±4.98	±0.10
3ml	311.91	36.10	23.86	81.79	34.70
(Dead; n=15)	±6.28	±0.63	±0.40	±3.63	±0.06

HR=heart rate, SBP=systolic blood pressure, MAP=mean arterial pressure, Resp=respiration rate, Temp=temperature, BPM=bit per mean.

A total 300 data sets were used to obtain the regression equation. Among the five parameters measured, the most contributing parameters to the survival rate were determined by obtaining correlation coefficients between the parameters values and the survival rates, as shown in Table II. Four parameters, except Temp, showed statistically significant correlation coefficients. Therefore, they were considered possible contributing parameters for the following logistic regression equation [12].

TABLE II
THE CORRELATION COEFFICIENTS BETWEEN PARAMETERS AND SURVIVAL RATE AND SIGNIFICANCES

Parameter	Correlation coefficient	p-value
HR*	-0.492	0.000
MAP*	0.733	0.000
SBP*	0.738	0.000
Resp*	0.612	0.000
Temp	0.077	0.248

HR=heart rate, SBP=systolic blood pressure, MAP=mean arterial pressure, Resp=respiration rate, Temp=temperature, BPM=bit per mean.
*$p < 0.01$

Forward selection method was initially applied to the four variables. We used the likelihood-ratio (LR) test to enter variables into the model. This involved estimating the model with each variable eliminated in turn and looking at the change in -2 log-likelihood when each variable is deleted. Four variables were entered into the training model before the forward selection procedure was terminated. Variables identified as significantly associated with survival rate were SBP, HR and Resp and included in the logistic regression model. MAP was excluded from the model because it is dependent on SBP. The Nagelkerke R-square value was 0.883. The H-L chi-square was 0.86 (degree of freedom=8, p=0.999). The following logistic regression equation predicting survival rates was obtained in (1). From left to right in (1), the contributing weight of the parameters to the evaluation survival rate decreases.

$$\mathbf{Survivalrate} = \mathbf{e}^{\mathbf{z}}/(1+\mathbf{e}^{\mathbf{z}})$$
$$\mathbf{Z} = -15.143 + 0.326 \times \mathbf{SBP} - 0.018 \times \mathbf{HR} + 0.024 \times \mathbf{Resp} \quad (1)$$

The ROC curve is shown in Fig.5. The performance of the model was quite good with an area under curve (AUC) of 0.99 and the optimal boundary value was calculated to be 0.25.

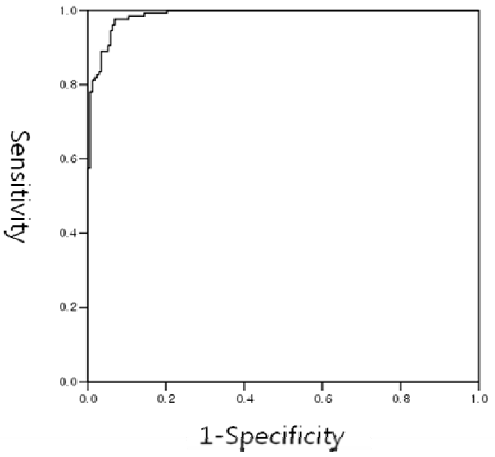

Fig. 5. ROC curve of a logistic regression equation

We tested the logistic regression equation for the other 150 data sets, and obtained the accuracy. Applying the determined optimal boundary value of 0.25, the accuracy was 94.7%.

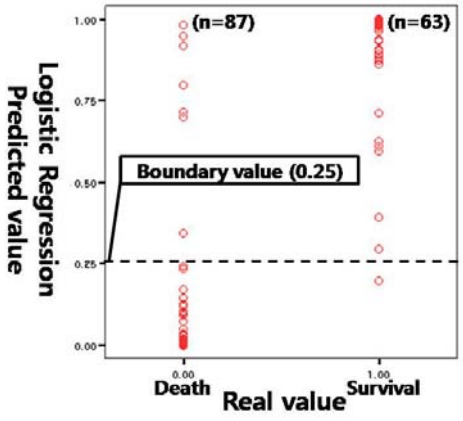

Fig. 6. Logistic regression equation value dispersion plot

IV. Discussion and conclusion

There is a previous study predicting survival rates in trauma [13]. It used six physiological variables such as heart rate, systolic blood pressure, temperature, respiratory rate, hematocrit, and Glasgow Coma Scale. However, we just used three parameters such as SBP, HR and Resp, and obtained very high value of AUC (0.99) even without any blood analysis. We have tried to measure SaO_2 of rat's tail using a pulse oximeter in vain

As this logistic regression equation predicts quite accurate survival rates of rats upon hemorrhagic shock with simple measurements of SBP, HR, and Resp, it could provide early diagnosis and effective treatment if this equation is applicable to human.

Especially, in the case of a shortage of medical staff during war or disaster, this study might be helpful for determining the priority of treatment. Therefore, future study would be focused on how we can apply these results from rats to human.

References

[1] CJ Murray and AD Lopez, *Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions*, Harvard University Press, Boston, 1996.

[2] CJ Murray and AD Lopez, "Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study," *Lancet*, vol. 349, pp. 1498–1504, 1997.

[3] CD Deakin and IR Hicks, "AB or ABC: pre-hospital fluid management in major trauma," *J Accid Emerg Med*, vol. 11, pp. 154–157, 1994.

[4] I. B. Chang, "Analysis of causes of death of the patients with multiple traumas who died in emergent department," *Annu. Meet Korea Neurosurg Soc*, Seoul, Korea, Nov. 2007.

[5] J. Markovchick, T. Pons, *Emergency medicine secrets, 4th edition*, Philadelphia, PA: Mosby, 2006, pp. 28-32.

[6] Martel MJ, MacKinnon KJ, Arsenault MY, Bartellas E, Klein MC, Lane CA, Sprague AE, and Wilson AK, "Hemorrhagic shock," *J Obstet Gynaecol Can.*, vol. 24, no. 6, pp. 504-511, 2002.

[7] Collins. T, "Understanding Shock," *Nursing Standard*, vol. 14, no. 49, pp. 35-41, 2000.

[8] M. Wilson, DP. David, and R. Coimbra, "Diagnosis and monitoring of hemorrhagic shock during the initial resuscitation of multiple trauma patients: a review," *J Emerg Med*, vol. 24, pp. 413-422, 2003.

[9] Akira Takasu, Toshihisa Sakamoto, and Yoshiaki Okada, "Effect of Induction Rate for Mild Hypothermia on Survival Time During Uncontrolled Hemorrhagic Shock in Rats," *J TRAUMA*, vol. 61, pp. 1330-1335, 2006.

[10] Ottenbacher KJ, Smith PM, Linn RT, Fiedler RC, Granger CV, "Comparison of logistic regression and neural networks to predict rehospitalization in patients with stroke," *J Clin Epidemiol*, vol. 54, no. 11, pp. 1159-1165, 2001.

[11] Eftekhar B, Mohammad K, Ardebili HE., Ghodsi M, Ketabchi E, "Comparison of artificial neural network and logistic regression models for prediction of mortality in head trauma based on initial clinical data," *BMC Med Inform Decis Mak*, vol. 5, no. 3, pp. 3, 2005.

[12] SC Kim, KC Nam, DK Rah, EJ Cha, DW Kim, "Assessment of the cleft nasal deformity using a regression equation," *Cleft Palate Cranifac J*, vol. 46, no. 2, pp. 197-203, 2009.

[13] DiRusso SM, Sullivan T, Holly C, Cuff SN, Savino J, "An artificial neural network as a model for prediction of survival in trauma patients: validation for a regional trauma area," *J Trauma*, vol. 49, no. 2, pp. 212-220, 2000.