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외상 환자에서 안정화된 생체 징후에 대한 정의의 다양성: 전국적인 조사 결과

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문성표, 유영선

- Abstract -

Diversity of the Definition of Stable Vital Sign in Trauma Patients: Results of a Nationwide Survey

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Purpose: Stable vital signs (SVSs) are thought to be the most important criteria for successful non-operative management (NOM) of blunt spleen injury (BSI). However, a consistent definition of SVSs has been lacking. We wanted to evaluate the diversity of the definitions of SVSs by using a nationwide survey.

Methods: A questionnaire regarding the definition of SVSs was sent to the trauma surgeons working at the Department of Trauma Surgery and Emergency Medicine at a level-I trauma center between October 2011 and November 2011. Data were compared using analyses of the variance, *t*-tests, χ^2 tests and logistic regressions.

Results: Among 201 surgeons, 198 responded (98.2%). Of these 198 responses, 45 were incomplete, so only 153 (76.1%) were analyzed. In defining the SVSs, significant diversity existed on the subjects of type of blood pressure (BP), cut-off value for hypotension, technique for measuring BP, duration of hypotension, whether or not to use the heart rate (HR) as a determinant, cut-off value of hypotension when the patient had a comorbidity or when the patient was a child. Of the 153 surgeons whose responses were analyzed, 91.5% replied that they were confused when defining SVSs.

Conclusion: Confusion exists regarding how to define SVSs. Most surveyed surgeons felt that a need existed to clarify both the definition of SVSs and the use of SVSs to determine hemodynamic stability for NOM. [J Trauma Inj 2014; 27: 115-25]

Key Words: Stable vital sign, Definition, Diversity, Blunt spleen injury

I. Introduction

Korea has a short history for emergency medical service system. The Korean Society of Emergency Medicine was established in 1989. Amendments on the laws of the emergency medical system were

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done in 1993. In 2000, a national emergency medical center was created. Currently, there are sixteen level I trauma centers, ninety eight level II trauma centers, and 325 level III trauma centers. Trauma is still a major cause of death in young people under 50. Blunt abdominal injury is common in trauma patients. The spleen is the most frequently injured organ in blunt abdominal trauma and hemorrhagic shock is the main cause of death. When hemoperitoneum caused by spleen injury was detected by diagnostic peritoneal lavage (DPL), exploratory laparotomy was usually performed.1 However, with the increased use of computerized tomography scanning (CT) and focused assessment with sonography for trauma (FAST), nonoperative management (NOM) of blunt spleen injury (BSI) was introduced, and is being actively used in many countries including Korea.(2-4) Most surgeons agree that cautious selection of the patient is fundamental for the success of NOM in BSI. Many selection criteria have been suggested and evaluated for this purpose and examples are vital sign, FAST, CT scan, injury scale or laboratory tests. (5-7)

Stable vital signs (SVSs) is thought to be the most useful criteria. However, a consistent definition of "SVSs" has been lacking. There is a possibility that surgeons are using a different determinant, numerical value, or obtaining method to define SVSs. We wanted to evaluate the diversity of the definition of SVSs by nationwide survey and provide the suggestion to clarify the definition of SVSs.

II. Materials and Methods

1. Questionnaire and Survey

A nationwide survey was performed between Oct 2011 and Nov 2011. The questionnaire was composed of 3 sections; 11 questions about biography, career, and circumstances of working environment, 14 questions about the definition of SVSs based on the simulated trauma case, and 7 questions about personal opinions regarding the definition of SVSs (Table 1). The questionnaire regarding the definition of SVSs was sent to the trauma surgeons working at the department of surgery and emergency medicine of level I trauma center. The survey was performed through email and an online survey program. It was analyzed under complete confidentiality.

2. Statistical analysis

Data were compared using analysis of variance (ANOVA) or t-test for continuous variables and x^2 test for categorical variables. Logistic regression was carried out to evaluate the variables which influence surgeons to make a diversity of SVSs.

III. Results

1. Section 1 of questionnaire

Among 201, 198 surgeons responded (98.2%). Forty five responses were incomplete and 153 responses were analyzed (76.1%). The average age of the respondents was forty six years old. 138 (90.2%) were male. sixty eight, fifty seven and twenty eight respondents were working at the level I, level II and level III trauma center respectively. They have been working for eighteen years on average. They were on duty for four days and treated three trauma patients per month. They performed emergent operations with the help of one surgical assistant. Sixty five (42.5%) were general surgeons, eighty eight (57.5%) were surgeons having other subspecialty. They were participating in less than one trauma conference per week (Table 2).

2. Section 2 of questionnaire

When defining SVSs, Sixty six (43.1%) of surgeons used only BP, sixty two (40.5%) used both BP and HR and eighteen (11.8%) used only HR (Fig. 1 and Table 3). Six surgeons were using respiratory rate or body temperature as an adjunct of determinant. Ninety five (62.1%) surgeons used systolic blood pressure (SBS) to define SVSs, forty five (29.4%) used mean arterial pressure (MAP) and thirteen (8.5%) diastolic blood pressure (DBP) (Fig. 2 and Table 3). Sixty three (41.2%) used manual technique to define SVSs, thirty seven (24.2%) preferred automated cuff, fifty (32.7%) had no preference (Fig. 3

Table 1. Details of the questionnaires.

Section 1. Biography, career and circumstances of working environment
1. How OLD are you?
2. What is your SEX?
① Male ② Female
3. How do you DEFINE your hospital?
① Special trauma center ② regional emergency center ③ local emergency center ④ local emergency institution
4. How LONG have you been working for the management of trauma patients?
5. How many DAYS are you on duty for trauma patient in a MONTH?
6. How many BEDS do you have in your hospital?
7. How many OPERATING ROOMS do you have in your hospital?
8. How many ASSISTANT (resident, nurse or technician) is assigned to the emergent operation?
9. How do you DEFINE yourself?
① general surgeon ② surgical fellow ③ surgeon who has other subspecialty ④ others
10. On average, how many TRAUMA PATIENTS do you treat a month?
11. On average, how often do you have regular medical CONFERENCE such as journal club, M & M and others about trauma a week?
Section 2. Definition of SVSs based on the simulated trauma case
50 years old male patient (170 cm/70 kg) fell down from 2 meter high ladder on his left frank area. The VS at ED admission were BP 90/60 mmHg, HR 120/minute, RR 20/minute, BT 37.5° C. GCS was 15 and the mental status was drowsy. There was no specific abnormality. 2 L of normal saline was infused rapidly while FAST revealed isolated spleen laceration and large amount of fluid around perirenal and perisplenic area. Secondary VS is being checked.
12. Which parameter (s) of VS (s) do you use as a determinant of your definition of hemodynamic instability? (BP: blood pressure, HR: heart rate, RR: respiration rate, BT: body temperature; check all that apply)
① BP ② HR ③ RR ④ BT
13. If you use RR as a determinant of hemodynamic instability, what is your lowest cut off value of HIGH respiratory rate to make you carry out emergent exploratory laparotomy? (/minute)
14. What KINDS of blood pressure do you use to determine the SVSs?
① SBS ② DBP ③ MAP ④ pulse pressure ⑤ others
15. What is your highest cut off value of HYPOTENSION to make you carry out emergent exploratory laparotomy? (Systolic BP, mmHg)
16. What kind of measuring TECHNIQUE do you use to decide if the patient is hypotensive?
① manual ② automated cuff ③ arterial line ④ at least two of them ⑤ all three of them ⑥ does not matter
17. How LONG do you feel the patient should be hypotensive before you to decide to carry out emergent exploratory laparotomy? (Minutes)
18. Do you use HEART RATE as an independent determinant of exploratory laparotomy regardless of hypotension?
① Yes ② No
19. What is your cut off value of TACHYCARDIA to make you carry out emergent exploratory laparotomy regardless of hypotension? (/minute)
20. Which of following statements do you support?
① carry out emergent laparotomy when BOTH blood pressure and heart rate are unstable
② carry out emergent laparotomy when ONE of blood pressure or heart rate is unstable
21. Do you have a different cut-off value of hypotension in case the patient has been taking medication which affects vascular system such as antihypertensives or anticoagulation?
① Yes ② No
22. Do you have different cut-off value of hypotension in case the patient has medical condition such as hypertension, diabetes, asthma etc?
① Yes ② No
23. If the patient is 5 to 15 year old children, do you feel like to use the different cut off value contrary to the adult's for the emergent laparotomy?
① Yes ② No

(continue)

Table 1. Details of the questionnaires. (continued)

Section 2. Definition of SVSs based on the simulated trauma case

24. If the patient is 5 to 15 year old children, what is your cut off value of blood pressure that makes you carry out emergent laparotomy? (mmHg)
25. If the patient is 5 to 15 year old children, what is your cut off value of heart rate that makes you carry out emergent laparotomy? (/minute)

Section 3. Personal opinions about the definition of SVSs

26. Do you use a BASE DEFICIT as an independent determinant to carry out emergent exploratory laparotomy regardless of hemodynamic instability?
    ① Yes ② No
27. Do you use a serum lactate level as an independent determinant to carry out emergent exploratory laparotomy regardless of hemodynamic instability?
    ① Yes ② No
28. Do you feel like to carry out emergent laparotomy when the patient has high grade spleen injury (grade IV or V) although the patient is hemodynamically stable?
    ① Yes ② No
29. Do you agree to use classic concept of hemodynamic instability (BP $\leq$ 90 mmHg AND HR $\geq$ 100/min) in order to decide the necessity of exploratory laparotomy
    ① strongly agree ② mildly agree ③ neutral ④ mildly disagree ⑤ strongly disagree
30. What is the reason you agree to use the classic definition of hemodynamic instability? Because, _____
    ① I believe it is evidence based medicine
    ② I have learned like that from my senior, medical conference, textbook etc
    ③ the range seems to be optimal
    ④ Others ( )
    ⑤ do not agree
31. Do you feel the need to have more clear and objective parameter to determine to carry out exploratory laparotomy in spleen injury?
    ① strongly agree ② mildly agree ③ neutral ④ mildly disagree ⑤ strongly disagree
32. Do you have any comments? ( )

Table 2. The results of Section 1 questionnaire (No=153).

Characteristics	Mean (range) or No (percentage)	*p*
Age (year)	46.7 (28 - 62)	
Sex		
Male	138 (90.2)	<0.01
Female	15 (9.8)	
Hospital		
level I TC*	68 (44.4)	
level II TC	57 (37.3)	
level III TC	28 (18.3)	
Career (year)	18 (3-31)	
Date of on duty per month (day)	4.6 (2-31)	
NO† of Beds	157 (25-1,500)	
NO of OR†	12.4 (2-50)	
NO of Surgical assistant	1.2 (0-2)	
Definition of self		
general surgeon	65 (42.5)	
surgeon with other subspecialty	88 (57.5)	
NO of New trauma patients	3.1 (0-15)	
NO of trauma conference per week	0.8 (0-3)	

* TC: trauma center, † NO: numbers, † OR: operating room

and Table 3). They thought emergent laparotomy (EL) should be carried out when SBS was equal or below 94 mmHg on average. 73% located between 80 to 99 mmHg and the cut off value of hypotension was ranged widely from 59 and 104 mmHg (Fig. 4 and Table 3). The duration of hypotension to make them carry out EL was 1.5 minutes (0~30 minutes). Thirty seven (24.2%) used heart rate (HR) as independent determinants of hemodynamic stability. On average, they thought EL should be carried out when HR was equal or above 109/minute. Sixty six (43.1%) used a different cut off value of BP when the patient had been taking vasoactive medicine. Seventy seven (50.3%) of the respondents used a different value of BP when the patients had medical comorbidity. 126 (82%) used a lower cut-off value of hypotension to define SVSs in pediatric patients and the value of BP was distributed from 60 to 99 mmHg. On average, they thought EL should be carried out when BP was equal or below 85 mmHg or

Table 3. The results of Section 2 questionnaire.

Characteristics	Mean (range) or No (%)	*p*
Determinants to define SVSs		
BP*	66 (43.1)	
HR†	18 (11.8)	
RR†	0 (0)	
BT§	0 (0)	
BP and HR	62 (40.5)	
BP and RR	2 (1.3)	
BP and BT	4 (2.6)	
Others	1 (0.7)	
Favorite BP to define SVSs‖		
SBP¶	95 (62.1)	<0.05
DBP**	13 (8.5)	
MAP††	45 (29.4)	
PP††	0 (0)	
Others	0 (0)	
Cut off value of BP to carry out EL§§	94 (59-104)	
Technique to check BP to define SVSs		
manual	63 (41.2)	
automated cuff	37 (24.2)	
arterial line	3 (2.0)	
do not care	50 (32.7)	
Duration of hypotension (minutes) to define as SVSs	1.5 (0-30)	
Using HR as independent determinants		
Yes	37 (24.2)	
No	116 (75.8)	
Cut off value of HR to carry out EL	109 (100-130)	
Using different value in case taking vasoactive agents		
Yes	66 (43.1)	
NO	87 (56.9)	
Using different value in case having medical comorbidity		
Yes	77 (50.3)	
No	76 (49.7)	
Using different value to define SVSs in pediatrics		
Yes	126 (82.4)	<0.01
No	27 (17.6)	
Cut off value of BP to carry out EL in pediatrics	85 (60-99)	
Cut off value of HR to carry out EL	119 (110-150)	

* BP: blood pressure, † HR: heart rate, ‡ RR: respiratory rate, § BT: body temperature, ‖ SVSs: stable vital sign, ¶ SBP: systolic blood pressure, ** DBS: diastolic blood pressure, †† MAP: mean arterial pressure, ‡‡ PP: pulse pressure, §§ EL: emergent laparotomy

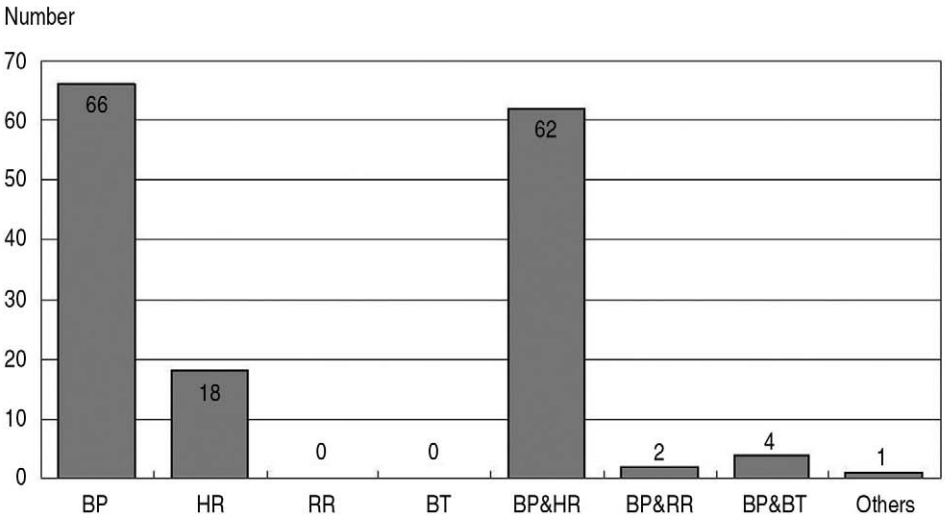

Fig. 1. Determinants to define stable vital sign.
BP: blood pressure; HR: heart rate; RR: respiratory rate; BT: body temperature

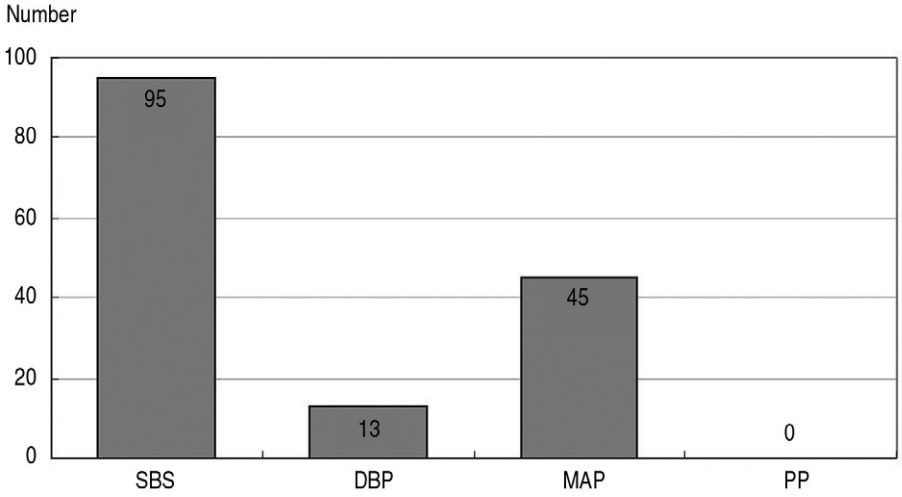

Fig. 2. Favorite type of the blood pressure to define stable vital sign.
SBS: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, PP: pulse pressure

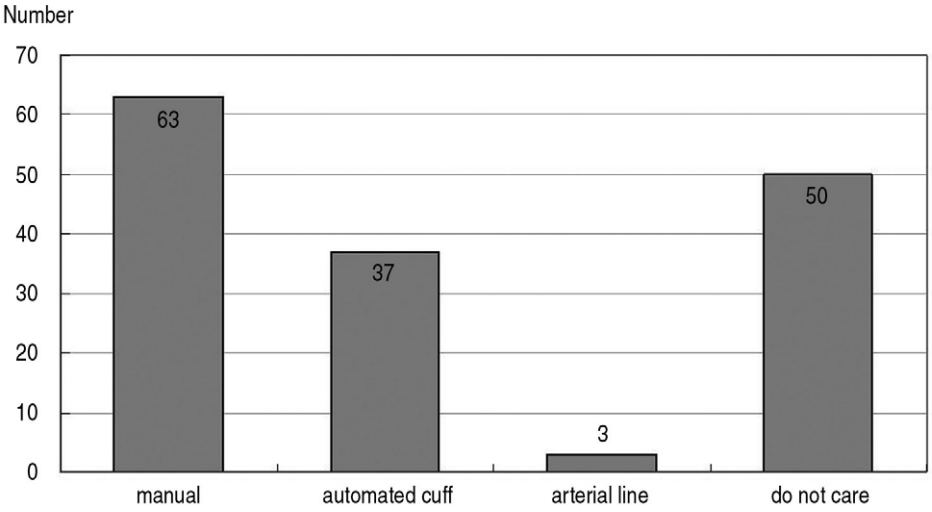

Fig. 3. Favorite technique to check the blood pressure to define stable vital sign.

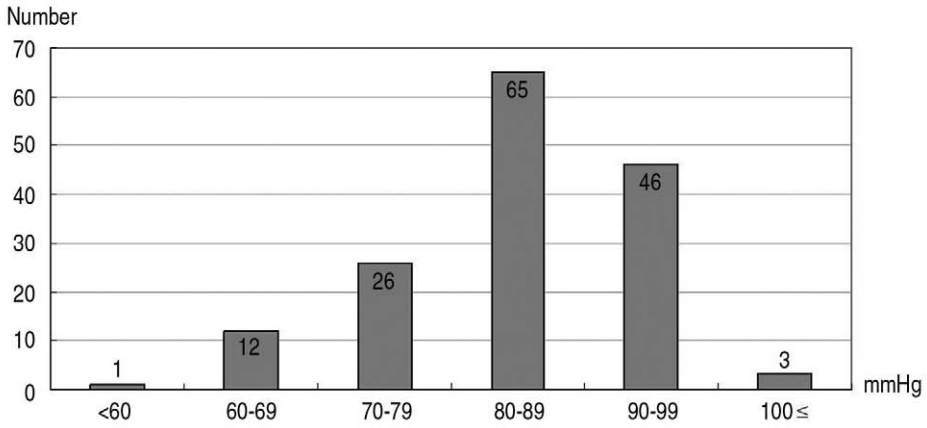

Fig. 4. Highest systolic blood pressure to carry out emergent laparotomy.

HR equal or above 119/minute (Table 3).

3. Section 3 of questionnaire

139 (90.8%) surgeons did not use base deficit or lactic acid as determinants of SVSs. Ninety seven (63.4%) replied they would not perform EL even when the injury grade was high as long as the patient was hemodynamically stable. Sixty one (39.9%) agreed to use the classic definition of hypotension; BP lower than 90 mmHg. Thirty nine (25.5%) replied they were using the classic definition because they thought it is evidence based medicine. Forty one (26.8%) used the classic definition because they were educated to use it. 130 (91.5%) surgeons who replied 'strongly agree' and 'mild agree' to the question on necessity of objective parameters were confused defining SVSs (Table 4).

4. Univariate and multivariate analysis

In univariate analysis, factors that were significantly associated with respondents who define SVSs differently with the classic definition were surgeons who were younger (<40 year old), female, working at level III trauma center, short career (<5 year). Only not agreeing to use the classic definition of SVSs was significant in multivariate analysis (Table 5).

IV. Discussion

When there is intraperitoneal hemorrhage from BSI, surgeons have to decide whether they operate on the patient or not. Before the 1980s, operative treatment was prevalent regardless of the severity of spleen injury. However, some surgeons observed that patients could be cured by NOM and tried to find the criteria for successful outcomes of nonoperative treatment.(1,8,9)

The first suggested determinant was radiologic findings. McKenney et al suggested a unique hemoperitoneum score system calculated by FAST. They calculated the depth in centimeters of the largest collection from the abdominal wall plus the total additional areas positive for fluid. 40 of 46 patients (87%) with score ≥3 required a therapeutic laparotomy. 46 of 54 patients (85%) with score <3 did not need operative intervention. The sensitivity of the score in determining the need for therapeutic operation was higher than systolic blood pressure (83% vs 28%).10 Starnes et al reviewed the role of computed tomography (CT) grade in NOM of BSI. The only significant difference between the success and failure of NOM was CT grade (1.47 vs 3.5; p= 0.0001). Although the amount of hemoperitoneum and the grade of injury are useful to evaluate the severity of the patients, it is usually neglected as long as the patient is stable. The radiologic findings cannot be a absolute contraindication for NOM nowadays. In our survey, 63.4% did not consider the amount of hemoperitoneum as a determinant of NOM. It is well accepted to perform NOM regardless of the radiologic findings.

SVSs was evaluated vigorously in many studies which tried to find the selection criteria for NOM. Longo et al reviewed sixty patients who were man-

aged successfully with NOM. They concluded that hemodynamic stability after initial fluid challenge is useful predicting factor. Although they prioritized hemodynamic stability (HS) in initial decision-making, they did not describe the definition of SVSs.(11) Lynch, Wasvary and Siplovich also did not describe the definition of SVSs.(12,13) Some studies described the definition of SVSs but the numeric value is frequently different. They defined SVSs as BP≥90 mmHg,(14-18) ≥100 mmHg,(19,20) and ≥110 mmHg.(21) Besides the numeric value, the type of BP and the measuring technique of BP are the other diver-

Table 4. Results of Section 3 questionnaire.

Categories	Number (%)	*p*
Using base deficit to define SVSs		
Yes	14 (9.2)	
No	139 (90.8)	<0.01
Using lactic acid to define SVSs		
Yes	12 (7.8)	
No	141 (92.2)	<0.01
Carrying out EL* based on radiologic finding		
Yes	56 (36.6)	
No	97 (63.4)	<0.05
Agreeing to the classic definition of SVSs		
strongly agree	28 (18.3)	
mildly agree	33 (21.6)	
neutral	47 (30.7)	
mildly disagree	27 (17.6)	
strongly disagree	18 (11.8)	
Reason to agree to classic definition of SVSs		
I believe it is evidence based medicine	39 (25.5)	
I have learned like that from my senior, medical conference, textbook etc	41(26.8)	
the range seems to be optimal	24 (15.7)	
Others	4 (2.6)	
do not agree	45 (29.4)	
Feeling the necessity to use other objective parameters		
strongly agree	75 (49.0)	<0.01†
mildly agree	65 (42.5)	
neutral	8 (5.2)	
mildly disagree	5 (3.3)	
strongly disagree	0 (0)	

* EL: emergent laparotomy

† comparison between agreeing group and disagreeing group

Table 5. Variables associated with the respondent who has cut off value different from classic definition of SVSs.

Variable*	Odds Ratio (95 % CI)†	
	Univariate Analysis	Multivariate Analysis
Age<40	1.23 (1.03-2.14)	0.48 (0.14-1.76)
Female Sex	1.12 (1.02-1.98)	0.13 (0.12-1.75)
Working at level III TC†	3.43 (2.16-4.65)	0.34 (0.32-1.87)
Short career less than 5 year	1.54 (1.17-2.56)	0.33 (0.14-1.36)
Do not agree to classic definition	8.65 (5.67-9.45)	4.67 (3.17-6.38)

* Only variables that were significant in the univariate analysis are listed.

† CI: confidence interval, † TC: trauma center

sity. There are basically 3 methods of measuring blood pressure; manual auscultatory method, automated cuff and arterial line. It is well known that there is a discrepancy between these methods.(22-24) In spite of the variability of the method of obtaining BP, most studies did not elucidate the method they used to determine SVSs. In our study, 62.1% used SBP to define SVSs. However, the others used MAP and DBP.

Another determinant of SVSs is heart rate (HR). Some authors included HR as a determinant while others did not (Table 6). Tachycardia appears earlier than hypotension in hypovolemic status. When a patient lost between 750 to 1500 ml of blood, BP is normal but HR increased to 100~120/min. Although postural pulse increment by postural change is a sensitive and specific marker of acute blood loss, it is difficult to apply to the trauma patients.(25) Tachycardia can result from pain, emotional status or heart problem regardless of volume status. This is why surgeons are hesitating to use HR as an independent determinant of SVSs. Only 24.2% used HR as an independent determinant of SVSs in our study.

Considering the duration of hypotension or tachycardia, the problem of diversity gets more complicated. Some surgeons decided EL as long as the patient is hypotensive at least once. Some are observing for 30 minutes (Table 3). However, there is no constant definition of the duration of hypotension or tachycardia to define SVSs.

When the patient had medical problems, defining SVSs is harder.(26) Confusion of defining SVSs also happens when the patient has spinal cord injury or when the patient had been taking vasoactive medication.(27)

Most surgeons are agreeing to use lower cut off value of hypotension to define SVSs for the pediatric patients but there was no study defining the numeric value of BP of SVSs according to the age of the patients. Many retrospective studies concluding that NOM in BSI of pediatric patients is more reasonable than adults actually failed to explain the definition of SVSs.(28,29) Much of the confusion and variabili-

Table 6. Studies that insist the usefulness of SVSs for successful NOM in BSI*.

Author	Year	study type	No of patients/Age (year)	Criteria for NOM†	Definition of SVSs‡
Longo	1989	retrospective	60/≥16	SVSs, transfusion < 4U age<50	None
William	1990	retrospective	16/all age	SVSs	SBP§ ≥90 mmHg
Lynch	1993	retrospective	48/unknown	SVSs, Class I, II and III	None
Archer	1996	retrospective	87/≥16	SVSs	SBP≥90 mmHg
Clancy	1996	retrospective	31/all age	SVSs, low injury severity score, CT scan	SBP≥90 mmHg
Wasvary	1997	retrospective	40/all age	SVSs, no evidence of decreased sensorium	None
Siplovich	1997	retrospective	55/≤14	clinical response to injury CT grade	None
Cathey	1998	retrospective	38/all age	SVSs, no multiple injuries, normal laboratory finding no transfusion	SBP≥100 mmHg and HR‖ ≤100/min
Konstantakos	1999	retrospective	147/all age	SVSs	SBP≥120 mmHg and HR≤95/min
Krause	2000	retrospective	18/≥55	SVSs, Transfusion<2 Unit No associated abdominal injury	SBP≥100 mmHg
Brasel	2003	retrospective	20/all age	SVSs	SBP≥90 mmHg and HR≤100/min
Watson	2006	retrospective	1392/all age	SVSs, Low grade	SBP≥90 mmHg

* BSI: blunt spleen injury, † NOM: nonoperative management, ‡ SVSs: stable vital sign, § SBP: systolic blood pressure, ‖ HR: heart rate

ty of the definition of SVSs is due to the diverse character of VS. Unfortunately prospective studies to define SVSs are unlikely to be performed to concern over patient's safety. We tried to find out the factors which influence surgeon to make the diversity of SVSs. Although young age, female sex, working at level III TC and short career seemed to be significant in univariate analysis, there was no significant factor in multivariate analysis. This means the problem of the diverse definition of SVSs is universal (Table 5).

Indicators of anaerobic metabolism such as arterial base deficit or lactate can be used to define SVSs. Bannon et al evaluated the efficacy of arterial base deficit and lactate concentration in trauma patients. They prospectively studied 40 patients with truncal injuries to examine the usefulness of central venous oxygen saturation (ScvO2), arterial lactate concentration, and arterial base deficit. Both base deficit and lactate concentration correlated with transfusion requirements; in addition, base deficit correlated with trauma score, and lactate correlated with the amount of hemoperitoneum.(30) Rixen et al also performed a prospective, multi-center, observational study of 2,069 multiple trauma patients to evaluate the significance of the base deficit (BD). BD was associated with a significant decrease in systolic blood pressure, prothrombin time, amount of transfusion and mortality. Their data showed that base deficit is an early available important indicator hemodynamic instability in trauma patients and predicted higher probability of death.(31-33) Base deficit and lactate are laboratory tests that can be available in the emergency room and can be important adjuncts in assessing SVSs in trauma patients.

Based on these studies, the society of emergency medicine and the society of traumatology in our nation made a guideline to use lactic acid and BD as a determinant of SVSs. Regardless of causes, the patient is defined hemodynamically unstable if four of following criteria meet.(34) (1) acutely ill-looked appearance or deterioration of mental status; (2) HR ≥100/minute; (3) RR≥22/min or $PaCO_2 \leq 21$ mmHg; (4) arterial BD≤−5 mEq/L or lactic acid≥4 mM/L; (5) urine out 〈0.5 ml/kg/hour; (6) hypotension (systolic blood pressure 〈 90 mmHg) lasts longer than 20 minutes. In order to use SVSs as a determinant of NOM in trauma patients, the diversity of the definition of SVSs should be minimized and more objective determinant should be provided.

V. Conclusion

Surgeons are using different definitions of SVSs for patients with BSI. There is confusion regarding how to define which patient has SVSs. Most surveyed respondents feel there is a need to clarify SVSs and how it should be used to determine HS for NOM. Using patients' symptoms and signs, base deficit and lactic acid can minimized the diversity and help the decision making process.

CONFLICT OF INTEREST STATEMENT

Seongpyo Mun, Young Sun Yoo declare that they have no conflict of interest.

IRB INSPECTION

This study was judged by Chosun IRB and approved. (IRB NO: 2013-03-05)

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