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Global longitudinal strain changes during hemorrhagic shock: An experimental study

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Abstract:

OBJECTIVES: Global longitudinal strain (GLS) appears sensitive and reproducible to identify left ventricular systolic dysfunction. The main objective was to analyze the GLS changes in an anesthetized-piglet model of controlled hemorrhagic shock (HS). The secondary objective was to evaluate if GLS changes was different depending on the expansion fluid treatment with or without norepinephrine.

METHODS: Eighteen anesthetized and ventilated piglets were bled until the mean arterial pressure reached 40 mmHg. Controlled hemorrhage was maintained for 30 min before randomizing the piglets to three resuscitation groups: control group, LR group (resuscitated with lactated ringer), and NA group (resuscitated with lactated ringer and norepinephrine).

RESULTS: There was no difference in the baseline hemodynamic, biological, and ultrasound data among the three groups. During the hemorrhagic phase, the GLS increased significantly from 25 mL/kg of depletion. During the resuscitation phase, the GLS decreased significantly from 20 mL/kg of fluid administration. There was no difference in GLS variation among the groups during the hemorrhagic, maintenance, and resuscitation phases.

CONCLUSION: In our HS model, GLS increased with hemorrhage and decreased during resuscitation, showing its preload dependence.

Keywords:

Hypovolemia, strain, systolic function

Introduction

Conventional techniques for determining systolic function are based on volume changes or visual assessment of wall motions; strain echocardiography measures tissue deformation within the

myocardium.^[1] The acquisition method used by strain to derive global longitudinal strain (GLS) appears more sensitive and more reproducible than left ventricular (LV) ejection fraction to identify LV systolic dysfunction.^[2] In addition, some studies have suggested that GLS may become a major parameter for the detection and prognostic assessment of patients with diastolic dysfunction.^[3] GLS is feasible in

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Box-ED

What is already known on the study topic?

Global longitudinal strain (GLS) is used in acute care patient for the ventricular systolic function evaluation

What is the conflict on the issue? Has it importance for readers?

In a shock state, when assessing myocardial function, hypovolemia is often one of the causes of the state of shock.

How is this study structured?

This was an experimental study in an anesthetized-piglet model of controlled hemorrhagic shock.

What does this study tell us?

GLS does not only vary with myocardial function. GLS varies with blood volume. A GLS alteration in a shock state may be due (completely or partially) to hypovolemia.

emergency patients and some authors believe that it should be considered for inclusion in the Emergency Ultrasound Fellowship curriculum.^[4] Given the formula for calculating the GLS, it could vary according to the blood volume. The use of GLS in acute patients to assess cardiac function is therefore in full development and we wonder if its values are not dependent on blood volume.

Hemorrhagic shock (HS) reduces tissue perfusion and oxygen delivery, leading to cellular dysfunction and multiple organ failure.^[5] The first line of HS treatment is to restore circulatory stability with rapid fluid administration and many studies suggest that vasopressors may be beneficial to treat.^[6,7] In the presence of life-threatening hypotension, administration of vasopressors, particularly norepinephrine (NE), is recommended in addition to fluids to maintain target arterial pressure.^[8]

The main objective of this study was to analyze the GLS changes in an anesthetized-piglet model of near-fatal controlled hemorrhage. The secondary objective was to evaluate if GLS changes were different depending on the expansion fluid treatment with or without NE.

Methods

Materials

This study was designed as a prospective, randomized, unblinded trial in a piglet model. The Animal Care and Use Committee of Languedoc-Roussillon (CEEA-LR-12013) approved the protocol and all experiments were performed in an authorized animal research laboratory. This animal study was conducted according to the European Directive 2010/63/EC regulating the use of animals in science. All facilities and transport comply with current legal requirements. Our hypothesis was that GLS values were dependent on blood volume. Thus, in

a HS model, GLS would increase with hemorrhage and decrease with fluid loading.

Animal preparation

Eighteen piglets of about 30 kg were included. The piglets used were large, white females, about 2½ months old. Animals were fasted overnight with free access to water. The piglets were premedicated by i.m. injection of ketamine 10 mg/kg, atropine 0.05 mg/kg, and midazolam 1 mg/kg. Anesthesia was induced with a bolus dose of propofol (4 mg/kg) and cisatracurium (0.25 mg/kg) via an ear vein. Anesthesia was maintained with propofol (8 mg/kg/h) and neuromuscular block was achieved with cisatracurium (0.5 mg/kg/h). After surgical tracheostomy (6.5 tracheal tube Tyco®, Atlanta, GA, USA), animals' lungs were ventilated with an inspired fraction of oxygen of 0.21, a tidal volume of 8 mL/kg, and a positive end-expiratory pressure of 5 cm H₂O.

Once the piglets were anesthetized, a 7 French double-lumen catheter was inserted with ultrasound guidance through the internal jugular vein into the right atrium. The central venous line was used to monitor central venous pressure and to inject cold boluses for transpulmonary thermodilution. A 5 French arterial catheter with an integrated thermistor tip was inserted through the femoral artery (PiCCO® Plus; Pulsion Medical Systems, Munich, Germany) and into the descending aorta for continuous arterial pressure monitoring, arterial blood sampling, and cardiac output (CO) transpulmonary thermodilution measurement. Stroke volume (SV) was calculated as follows: CO (by thermodilution)/heart rate (HR). The femoral vein was also cannulated with an 8.5 French catheter (Arrow®, Arrow International, Inc., Cleveland, OH, USA) for blood withdrawal and for the administration of resuscitation fluids. All pressure-measuring catheters were connected to transducers (PiCCO® Plus) for continuous recording of systemic arterial pressure, HR, and temperature.

Experimental protocol and measurement times

The study design shown in Figure 1 has already been published.^[9,10] T₀ was the start of the experiment; the measured mean arterial pressure (MAP) was considered the reference MAP. T₁ was reached when MAP reached 40 mmHg. MAP was maintained for 30 min at 35–45 mmHg (T₂). The hemorrhage ended after T₂. Fluids could be administered or the bleeding could be continued for this objective. The piglet was then resuscitated until a MAP equal to its baseline MAP was reached. Finally, MAP was maintained at ±10% of the reference MAP for 1 h. Eighteen piglets were randomly allocated by sealed envelopes into three groups based on the type of resuscitation. Until T₂ [Figure 1], the procedure was the same for the three

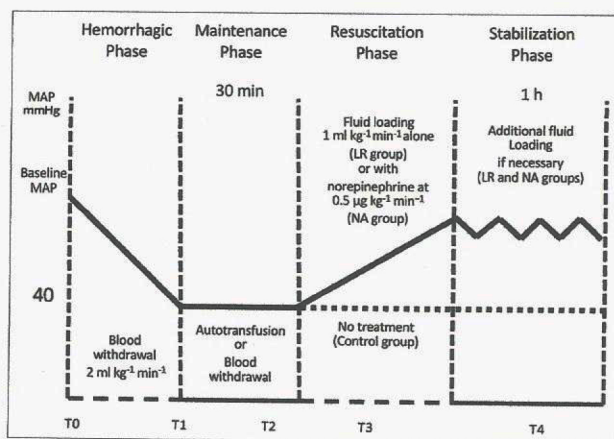


Figure 1: Study design. MAP: Mean arterial pressure

groups. The control group ($n = 6$) was just monitored and neither treatment was administrated. As there was no resuscitation phase in this group, the T3 time did not exist and the T4 time after 1 h of MAP was between 35 and 45 mmHg. The LR group ($n = 6$) was resuscitated with lactated ringer's (LR) solution and the third group received LR and norepinephrine administration (NA; $n = 6$). NE was infused with a stable infusion rate of 0.5 $\mu\text{g}/\text{kg}/\text{min}$. Measurements were performed at every 5 mL/kg of bleeding during the hemorrhagic phase (T_{0a} , T_{0b} , etc.) and every 10 mL/kg of fluid infusion during the resuscitation phase (T_{2a} , T_{2b} , etc.). For the LR and NA groups, MAP was maintained at its baseline value $\pm 10\%$ by additional fluid infusion according to the allocated group for a further hour; then, all animals were killed using i. v. thiopental infusion (2 g). Hemodynamic parameters were transcribed from the PiCCO[®] monitor. CO was measured by transpulmonary thermodilution, extravascular lung water, and pulse pressure variation (PPV) by pulse contour analysis. Blood biochemistry values were analyzed at all times (T0–T4): arterial lactate, arterial pH, hemoglobin, plasma HCO_3^- , and plasma creatinine.

Conventional echocardiography

Images were obtained with a Vivid S70 ultrasound device (Vivid S70, GE Medical Systems, Milwaukee, WI, USA) equipped with a phased-array transducer (M5S). Velocity time integral of the subaortic blood flow (VTI) was computed on an apical five-chamber view using pulse Doppler in the left ventricle outflow chamber. The apical view was used to attain tissue Doppler across the mitral annulus. Pulse tissue Doppler imaging velocities were acquired at the lateral mitral annuli and included the peak systolic (s') velocity.

Strain echocardiography

Strain echocardiography measures actual tissue

deformation within the myocardium. The definition of strain (ϵ) is "the relative change in length of a material related to its original length."^[1] The strain calculation is based on the distance between two points in systole (L_{syst}) and in diastole (L_{diast}): $(\epsilon = (L_{\text{syst}} - L_{\text{diast}})/L_{\text{diast}})$.^[1,11]

Strain is a dimensionless measurement of deformation, expressed as a percentage change from an object's original dimension. In the present study, we measured only longitudinal strain because, in general, longitudinal LV mechanics, which are predominantly governed by the subendocardial region, are the most vulnerable component of LV mechanics and, therefore, are most sensitive to the presence of myocardial disease. We acquired two-dimensional gray-scale in the apical four-chamber for one cardiac cycle and stored the results digitally for subsequent off-line analysis using commercially available automated function imaging (AFI) software (EchoPAC Workstation, BT09, GE-VingMed, Horten, Norway). The peak systolic longitudinal strain was obtained from the apical four-chamber view using the AFI software, and the mean peak systolic longitudinal strain obtained from the standard apical four-chamber view was considered the global peak systolic longitudinal strain (GLS).

Statistical analysis

As no study had investigated the GLS changes in HS, no calculation of sample size was possible. Quantitative data were expressed as median with 25th and 75th percentiles (25th percentile–75th percentile). Qualitative variables were expressed as frequency with percentages. Comparison of quantitative variables among the different groups was performed by a nonparametric test (Mann–Whitney U -test or Kruskal–Wallis test if multiple classes were used). The relationship between two variables was tested by the Chi-square test or by the Fisher's exact test when Chi-square conditions of application (theoretical numbers < 5) were not met. Correlation coefficients were calculated to assess the relationship between GLS and PPV. The significance level was set at 5% for all tests. Statistical analysis was performed under R 3.3.3 (2017, R Foundation for Statistical Computing, Vienna, Austria).

Results

Animals and compliance with protocol

Eighteen piglets were randomly allocated to the control, LR, or NA group (six per group). All phases of the experiment were respected for all piglets.

Measures

On all piglets, 215 GLS measures were attempted and 178 were successful (83%). The success rates were, respectively, for T_0 , T_{0a} , T_{0b} , T_{0c} , T_{0d} , T_{0e} , T_1 , T_{1a} , T_2 , T_{2a}

T_{2b}, T_{2c}, T₃, T_{3a}, and T₄ as follows: 100%, 94%, 82%, 100%, 92%, 80%, 65%, 72%, 65%, 88%, 100%, 100%, 100%, 75%, and 74%. Weight, mean hemodynamic, and ultrasound data at the beginning (T₀) of the study and during T₁, T₂, T₃, and T₄ times are shown in Table 1. Table 2 shows necessary volumes for induced, maintained HS and for resuscitation and stabilization. The mean biological data at all times of measurements are given in Table 3.

Outcomes

GLS changes during the experiment for all groups are shown in Figure 2. Comparison between GLS and SV changes during hemorrhagic and maintenance phases is shown in Figure 3. The correlation coefficient between GLS and PPV was 0.27 (IC 95% [0.11; 0.41]; *P* < 0.01).

Figure 4 shows the comparisons of GLS changes and PPV.

Discussion

Main results

Our study shows that in a HS piglet model, GLS increases during hemorrhage and decreases during resuscitation. However, after 10 at 20 mL/kg of hemorrhage, GLS changes seem faster than SV and PPV.

This study describes for the first time the course of myocardial strain during hemorrhage. As a primary result, GLS is closely related to blood volume variation as it increases in response to blood removal and decreases

Table 1: Hemodynamic and ultrasound data at baseline (T₀), during hemorrhagic shock (T₁, T₂), and after fluid resuscitation (T₃, T₄) in the control, lactated ringer, and norepinephrine administration groups

	Control group (n=6)	Lactated ringer Group (n=6)	Norepinephrine administration Group (n=6)	P
Weight (kg)	31.0 (30.2-32.6)	29.1 (28.8-30.0)	29.7 (29.4-31.0)	NS
MAP (mmHg)				
T ₀	72 (68-81)	85 (77-93)	77 (64-84)	NS
T ₁	40 (35-40)	39 (38-40)	40 (40-42)	NS
T ₂	44 (41-44)	39 (36-44)	39 (35-44)	NS
T ₃		74 (55-80)	85 (70-91)	NS
T ₄	33 (25-42)	79 (71-85)	74 (61-81)	0.02
Cardiac output (L/min)				
T ₀	2.7 (2.5-4.1)	3.1 (2.8-3.2)	2.6 (2.3-2.9)	NS
T ₁	1.6 (1.6-1.9)	1.7 (1.5-1.7)	1.6 (1.4-1.8)	NS
T ₂	1.7 (1.5-2.0)	1.6 (1.6-2.0)	1.8 (1.2-1.9)	NS
T ₃		3.0 (2.8-3.5)	3.6 (2.7-4.7)	NS
T ₄	1.4 (1.1-1.7)	3.3 (3.2-3.4)	2.8 (2.5-3.1)	0.01
Heart rate (bpm)				
T ₀	111 (95-119)	102 (94-110)	91 (82-101)	NS
T ₁	164 (98-193)	187 (138-198)	159 (102-198)	NS
T ₂	178 (156-201)	188 (169-195)	144 (112-182)	NS
T ₃	-	169 (130-177)	148 (139-165)	NS
T ₄	161 (149-168)	155 (138-174)	172 (167-182)	NS
S' wave (cm/s)				
T ₀	10 (9-13)	10 (7-11)	12 (11-14)	NS
T ₁	8 (6-9)	8 (7-10)	11 (8-13)	NS
T ₂	7 (6-8)	8 (7-10)	10 (9-12)	NS
T ₃	-	11 (9-19)	14 (13-17)	NS
T ₄	6 (4-9)	19 (17-19)	13 (12-13)	0.04
Velocity time integral (cm)				
T ₀	11 (10-15)	12 (11-13)	14 (12-13)	NS
T ₁	10 (8-10)	11 (8-13)	11 (11-13)	NS
T ₂	8 (8-9)	11 (8-13)	10 (8-12)	NS
T ₃	-	15 (14-17)	17 (15-20)	NS
T ₄	8 (6-11)	16 (14-17)	17 (15-18)	0.05
Global longitudinal strain (%)				
T ₀	-10 (-12--6)	-13 (-15--7)	-14 (-15--7)	NS
T ₁	-4 (-8--3)	-8 (-9--6)	-5 (-7--5)	NS
T ₂	-5 (-5--5)	-5 (-11--5)	-7 (-8--5)	NS
T ₃	-	-16 (-18--16)	-15 (-18--13)	NS
T ₄	-4 (-6--4)	-15 (-16--14)	-9 (-11--5)	0.06

Data are expressed as median (Q1-Q3). NS: *P*>0.2. MAP=Mean arterial pressure, NS=Not significant

Table 2: Volumes of hemorrhage and resuscitation fluid (mL/kg) in the control, lactated ringer, and norepinephrine administration groups

	Control group (n=6)	Lactated ringer group (n=6)	Norepinephrine administration group (n=6)	P
T ₀ -T ₁ volume of hemorrhage	-25 (-30--20)	-30 (-38--26)	-23 (-29--16)	NS
T ₁ -T ₂ volume of hemorrhage or resuscitation fluid volume	-3 (-8--2)	-1 (-4-0)	0 (0-0)	0.09
T ₂ -T ₃ resuscitation fluid volume	-	26 (14-39)	15 (8-32)	NS
T ₃ -T ₄ resuscitation fluid volume	-1 (-2--1)	3 (0-14)	0 (0-4)	0.04

Negative volumes are bleeding volumes, positive volumes are fluid administration volumes. Data are expressed as median (Q1-Q3). NS: P>0.2. NS=Not significant

Table 3: Biological data at baseline (T₀), during hemorrhagic shock (T₂), and after fluid resuscitation (T₃, T₄) in the control, lactated ringer, and norepinephrine administration groups

Variables	Control group (n=6)	Lactated ringer group (n=6)	Norepinephrine administration group (n=6)	P
Arterial lactate (mmol/L)				
T ₀	2.1 (1.2-4.6)	1.4 (0.9-1.7)	1.9 (1.3-2.4)	0.14
T ₁	3.3 (2.1-4.8)	2.8 (1.8-3.2)	3.7 (2.8-5.6)	NS
T ₂	5.6 (3.8-6.5)	4.5 (3.3-6.8)	4.9 (3.0-8.8)	NS
T ₃		4.0 (2.7-5.3)	6.2 (4.3-7.2)	NS
T ₄	10.2 (5.8-12.9)	2.4 (2.0-3.5)	2.5 (2.1-3.9)	0.03
Arterial pH				
T ₀	7.50 (7.43-7.56)	7.49 (7.45-7.56)	7.49 (7.47-7.52)	NS
T ₁	7.51 (7.50-7.56)	7.50 (7.43-7.53)	7.49 (7.44-7.53)	NS
T ₂	7.49 (7.47-7.56)	7.42 (7.42-7.48)	7.50 (7.37-7.51)	NS
T ₃		7.48 (7.44-7.52)	7.46 (7.37-7.47)	NS
T ₄	7.48 (7.44-7.51)	7.50 (7.48-7.53)	7.49 (7.45-7.54)	NS
Hemoglobin (g/dL)				
T ₀	7.6 (7.1-8.4)	8.5 (7.2-9.3)	9.1 (8.6-9.3)	NS
T ₁	7.5 (6.1-7.7)	7.6 (7.1-8.4)	7.3 (7.1-7.4)	NS
T ₂	6.2 (5.6-7.1)	6.7 (5.8-7.9)	7.2 (5.5-7.5)	NS
T ₃		5.5 (4.4-6.9)	6.1 (5.4-6.6)	NS
T ₄	6.7 (6.0-6.8)	6.3 (5.6-6.6)	6.9 (5.7-7.9)	NS
Plasma HCO₃⁻ (mmol/L)				
T ₀	30.5 (28.1-31.9)	30.0 (28.1-32.3)	29.8 (26.9-32.3)	NS
T ₁	31.3 (29.6-33.4)	28.7 (27.6-30.6)	24.8 (22.9-27.7)	0.03
T ₂	27.0 (25.5-29.2)	26.7 (25.9-27.6)	23.4 (22.2-24.3)	0.09
T ₃		28.2 (26.0-31.1)	25.1 (24.8-25.7)	0.09
T ₄	23.0 (21.6-23.6)	30.5 (28.8-32.4)	28.3 (25.9-28.5)	0.04
Plasma creatinine (μmol/L)				
T ₀	97 (84-116)	121 (96-144)	134 (89-172)	NS
T ₁	109 (100-129)	134 (114-151)	135 (89-185)	NS
T ₂	115 (112-123)	154 (145-166)	128 (104-170)	NS
T ₃		142 (126-160)	122 (92-154)	NS
T ₄	179 (157-184)	126 (118-156)	107 (97-142)	NS

Data are expressed as median (Q1-Q3). NS: P>0.2. NS=Not significant

during blood volume compensation. Due to its first use in the cardiology setting, only a few studies have investigated the influence of preload on GLS. In patients with a low preload dependency, GLS was first described as independent of the preload.^[12] However, animal and human studies have underlined the influence of preload on GLS in hypovolemic subjects.^[13-15] This discrepancy between hypovolemic and nonhypovolemic patients can be explained by the formula of GLS $(L_{syst} - L_{diast})/L_{diast}$. Indeed, in all the patients, whatever their hemodynamical status, L_{diast} will be mechanically affected by loading

or unloading (end diastolic stretch of the myocardial fibers). Conversely, due to their position in the Frank-Starling curve, L_{syst} will be affected in preload-dependent patients only (preload induced changes in inotropism).^[15] Consequently, the variations of GLS due to the changes in preload will be amplified in hypovolemic patients. Hence, we tested both GLS and PPV at all stages of the experiment. Interestingly, we confirmed for the first time that PPV and GLS were correlated. In 2014, Cameli *et al.* emphasized the ability of atrial longitudinal strain to predict a PPV >15% in mechanically ventilated

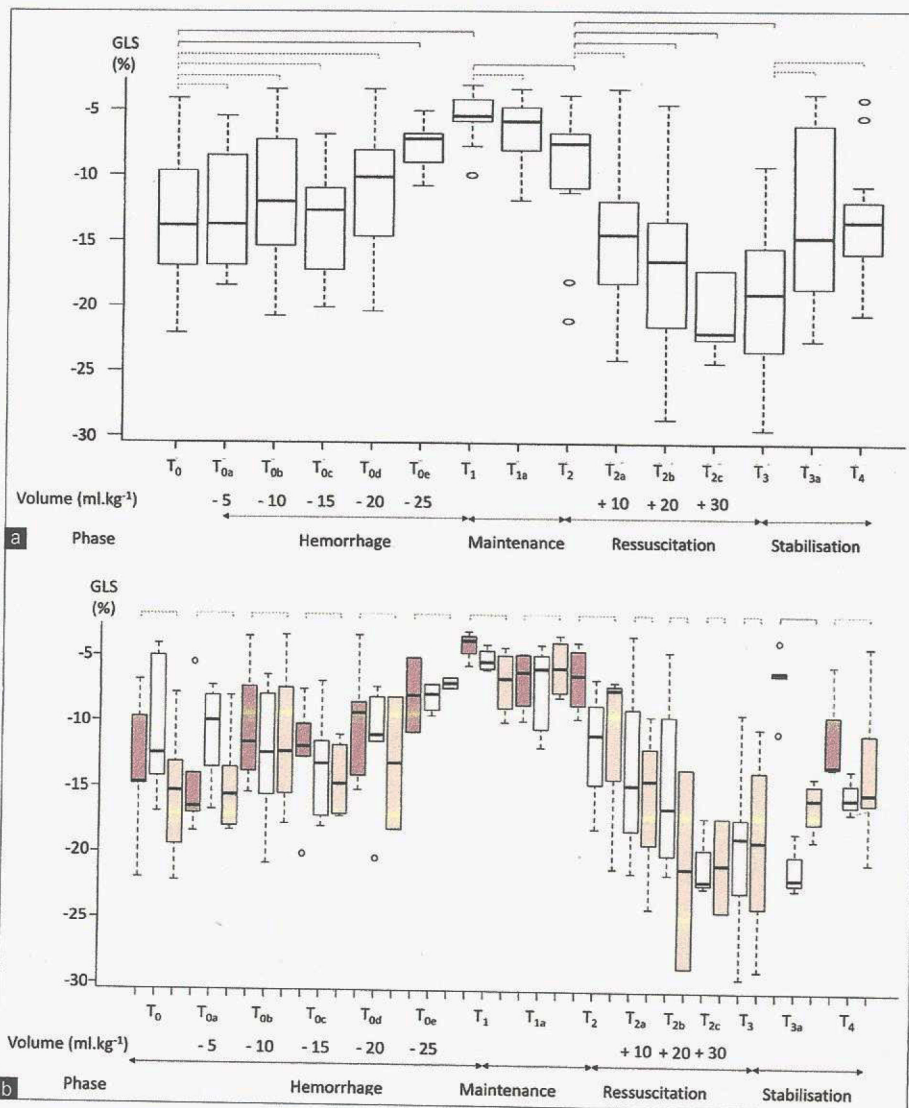


Figure 2: GLS changes for all groups. (a) GLS changes for all groups; (b) changes for each group; dark gray boxplots: control group; white boxplots: LR group; light gray boxplots: NA group; dashed square brackets: $P > 0.05$; solid lines square brackets: $P < 0.05$; GLS: Global longitudinal strain

patients.^[16] Nevertheless, the left atrial longitudinal strain reflects filling pressure (i.e., a static index) and probably less accurate than ventricular GLS variations for the prediction of fluid responsiveness. Future studies evaluating the ability of GLS variations after a change in preload to predict fluid responsiveness are, therefore, necessary. In clinical practice, interpretation of GLS values to assess cardiac function should be relevant only in patients with controlled blood volume.

NE is the recommended amine in HS states.^[8] Some animal studies have shown the positive effect of NE on myocardial performance.^[17,18] In our study, no significant difference was found between the LR and NA groups during the resuscitation phase for GLS changes.

We cannot know from this model if GLS is able to detect myocardial dysfunction in HS. It is likely that in our HS model, the shock state does not last long enough to induce significant myocardial dysfunction. However, the GLS aggravation after 10 at 20 mL/kg of depletion is more important than SV and PPV. Probably, the GLS does not vary only according to the preload in this model. These results will have to be completed in order to understand their meaning.

Limitations

First, the findings of the present study may not be extrapolated to trauma patients as no direct tissue damage was induced in this model. Second, NE was infused with a stable infusion rate of 0.5 $\mu\text{g}/\text{kg}/\text{min}$, which differs from usual clinical practice. Third, baseline

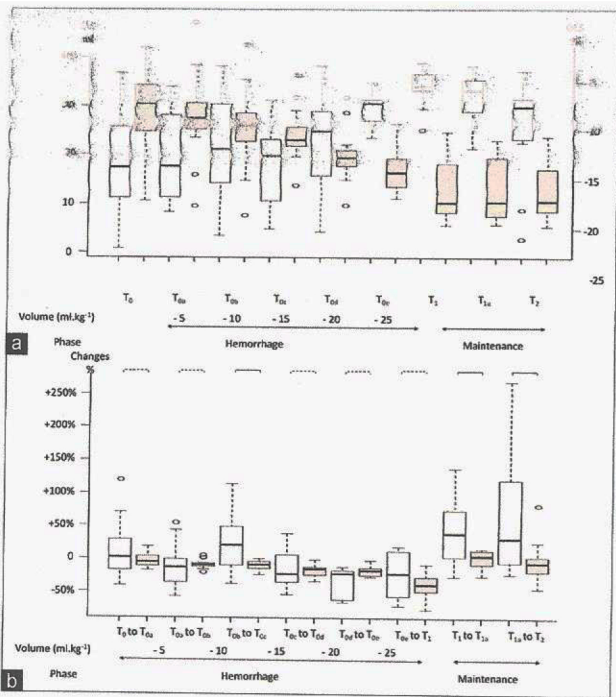


Figure 3: GLS and SV changes. (a) GLS and SV values in hemorrhagic and maintenance phase; (b) GLS and SV changes between all step in hemorrhagic and maintenance phase; white boxplots: GLS; gray boxplots: SV; dashed square brackets: $P > 0.05$; solid lines square brackets: $P < 0.05$; SV: Stroke volume; GLS: Global longitudinal strain

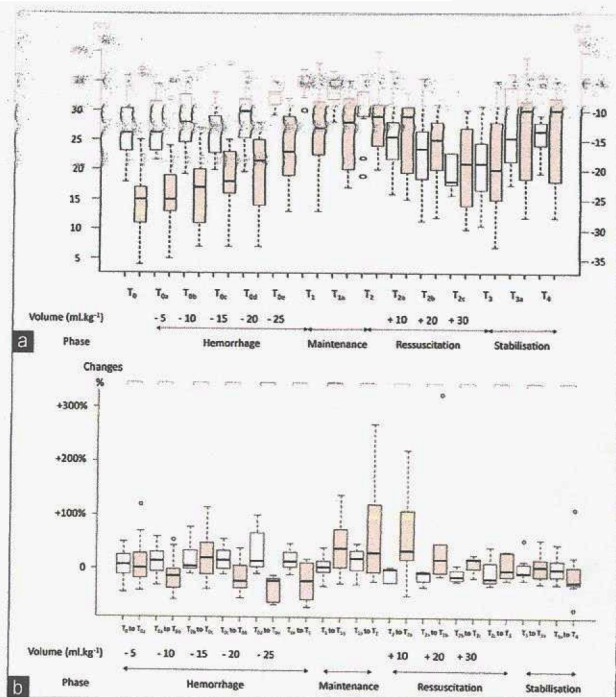


Figure 4: GLS and PPV changes. (a) GLS and PPV values; (b) GLS and PPV changes between all steps; white boxplots: GLS; gray boxplots: PPV; dashed square brackets: $P > 0.05$; solid lines square brackets: $P < 0.05$; GLS: Global longitudinal strain; PPV: Pulse pressure variation

arterial blood lactate appears to be lower in the LR group; we have no explanation and we do not think it influences the results. In addition, the use of a MAP-based HS modality results in a variation in the volume of hemorrhage to induce shock and the volume of infusion for resuscitation. Finally, GLS was evaluated by only a four-chamber view. However, there is a good correlation between GLS and the 4-chamber view strain values.^[15]

Conclusion

In this controlled HS model, GLS increased linearly with hemorrhage and decreased during resuscitation. These results confirm a preload dependency of GLS. During hemorrhage, GLS variations should not be interpreted as a variation of systolic function but rather as a consequence of hypovolemia.

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Author contributions statement

TM, LZ, LM, CR, and XB conceived and designed the experiments; TM,

CR, and XB performed the experiments; TM, LZ, PGC, LM, and XB analyzed and interpreted the data; TM and XB contributed reagents, materials, analysis tools, or data; TM, LZ, PGC, JELC, LM, JYL, CR, and XB wrote the paper.

Conflicts of interest

XB declares a competing interest as a US teacher for GE (GE MEDICAL SYSTEMS ULTRASOUND) customers. The other authors state they have no competing interests.

Ethical Approval

The Animal Care and Use Committee of Languedoc-Roussillon (CEEA-LR-12013) approved the protocol and all experiments were performed in an authorized animal research laboratory. This animal study was conducted according to the European Directive 2010/63/EC regulating the use of animals in science.

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