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Sepsis/Infection

Strong correlation between doppler snuffbox resistive index and systemic vascular resistance in septic patients

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ABSTRACT

Purpose: To compare systemic vascular resistance index (SVRI) as measured by invasive transpulmonary indicator dilution (TPID) and non-invasive Doppler-derived resistive index in septic patients.
Methods: We measured the snuffbox resistive index (SBRI) in both hands of septic patients who received hemodynamic monitoring by TPID prospectively.
Results: Thirty-six patients with septic shock were enrolled (median acute physiology and chronic health evaluation II score: 23; median age: 64 years). Four SBRI values were measured in each patient, for a total of 96 patient days and 951 ultrasound measurements. The correlation coefficients between SVRI and the four SBRI values were all higher than 0.87 ($p < .001$). A higher SVRI was associated with sharp waveforms and reversed diastolic flow. A resistive index (RI) of 0.97 was the lower limit of normal SVRI (1700 dyn*s*cm^{-5}*m^2), and an RI of 1.1 was the upper limit of normal SVRI (2400 dyn*s*cm^{-5}*m^2).
Conclusions: Using ultrasound to measure RI is a noninvasive, inexpensive, reliable method to evaluate peripheral vascular resistance in septic patients, and it is highly correlated with SVRI. In addition, SBRI can be used to evaluate peripheral circulatory disturbances in septic patients.

1. Background

Sepsis is defined as critical organ impairment caused by dysregulated host immunity to infection, and septic shock is defined as progression that results in persistent hypotension requiring vasopressors to maintain adequate tissue perfusion [1]. Sepsis and septic shock are the main causes of morbidity and mortality in critically ill patients, and they affect millions of people each year worldwide [2]. In hospitalized patients, the reported mortality rate due to sepsis and septic shock ranges from 33% to 50%, with even higher rates in intensive care units [3-5]. Because of the high rates of comorbidities and mortality, the management of sepsis is very important and includes the early detection and treatment of infections, hemodynamic instability, and impaired organs.

There are two different patterns of hemodynamics with regards to septic shock. The initial pattern is vasodilatation as indicated by the hemodynamics of a low systemic vascular resistance index (SVRI), which is usually accompanied with a normal or high cardiac index (CI). In general, SVRI is directly proportional to mean artery pressure, because SVRI is defined as mean artery pressure-central venous pressure)*80/cardiac index. Previous studies have demonstrated that SVRI is an early and important predictor of a poor prognosis in patients with septic shock, in that a lower SVRI is associated with increased mortality [6-9]. The American College of Critical Care Medicine (ACCM) and other studies suggest that when shock develops with a decreased SVRI, treatment with vasopressors with the aim of increasing the SVRI should be initiated, and hence elevating the mean arterial pressure is a mainstay of

Abbreviations: RI, resistive index; SBRI, snuffbox resistive index; SVRI, systemic vascular resistance index; CI, cardiac index; TPID, transpulmonary indicator dilution technique; SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; SB, snuffbox; SVR, systemic vascular resistance.

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treatment for septic patients [10-12]. When the hemodynamics change to a higher SVRI and low CI, vasodilation and inotropic agents such as dobutamine should be administered to reduce ventricular afterload and contribute to better cardiac output [10-12]. Therefore, a lower or higher SVRI indicates a disturbance in the peripheral circulation and is associated with poor outcomes [13,14].

Monitoring hemodynamics using transpulmonary indicator dilution (TPID) has increasingly been used due to less invasiveness, fewer complications, and ease of use [15]. Although TPID is less invasive, the technique still requires the use of catheters for the great vessels which can result in complications. Therefore, the development of a non-invasive method to assess hemodynamics is important. Doppler ultrasound is a non-invasive technique used to detect cardiac output and vascular resistance. Resistive index (RI) is resistance to blood flow caused by the vascular bed, and it can be used to represent vascular compliance. Previous studies have demonstrated that a Doppler-derived renal RI can be used as a predictor of clinical prognosis in many renal diseases [16,17]. Furthermore, Ban et al. demonstrated the correlation between Doppler snuffbox resistive index (SBRI) and SVRI as measured by TPID in 15 patients who received cardiac surgery [14]. However, no study has yet proven the utility of SBRI in septic patients. Therefore, the aim of this study was to compare Doppler SBRI and SVRI in septic patients.

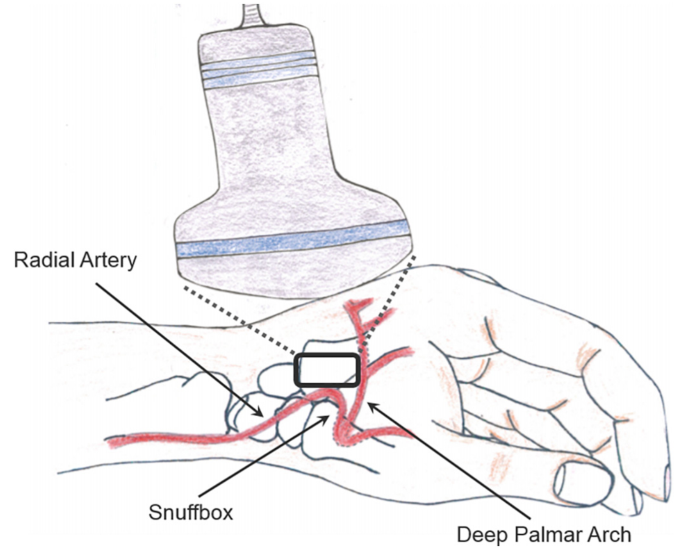

Fig. 1. Anatomy of the snuffbox. The black rectangular box represents the scanning site and plane for the snuffbox.

2. Methods

2.1. Study design and patients

From May 2017 to December 2017, we prospectively conducted this study in the medical intensive care unit of a 3000-bed tertiary hospital. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the guardians of all enrolled patients signed an informed consent form.

The inclusion criteria were patients aged >18 years admitted to our medical intensive care unit due to septic shock, defined as shock caused by a suspected or known infection [1]. The severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The hemodynamics of the enrolled patients were monitored using a PiCCO system (PiCCO, Pulsion Medical Systems, Munich, Germany).

2.2. Measurement of SBRI by ultrasound

SBRI was measured using a PHILIPS (CX50 POC) portable system with a 3–10-MHz linear probe and resolution limit of 0.01 mm. The evaluation of RI via Doppler was performed as previously described (Fig. 1) [14,16,17]. The radial artery was chosen as the target artery in the snuffbox (SB) as it is a peripheral artery in which the incidence angle between the ultrasound beam and blood flow direction is smallest, and thus can reduce errors [14]. We measured the SBRI at four points, including two depths (1 cm and 1.5 cm) of the radial artery in the SB in both hands. The SBRI was imaged in B mode using waveform analysis, and was defined as follows: resistive index = (peak systolic velocity–end diastolic velocity)/peak systolic velocity. This index has been shown to be a feasible and accurate parameter for evaluating vascular resistance and vascular compliance [18,19].

To evaluate the repeatability and reproducibility of the SBRI measurements, three measurements were conducted within 30 min in patients with a stable hemodynamic status in 1 day for 3 consecutive days, and the three measurements were compared with three simultaneous values of SVRI. Two skilled intensivists conducted a total of 30 measurements on five septic patients in the MICU to evaluate interobserver reproducibility.

2.3. Data collection

Demographic and clinical data of the patients were collected. We performed ultrasound measurements for 3 consecutive days after the PiCCO system had been set-up in each patient. At the same time points, the daily measurements and the simultaneous values of SVRI from the PiCCO system were recorded.

2.4. Statistical analysis

The demographic data of the patients were presented as mean ± standard deviation (SD), or number (percentage). The intraobserver repeatability and interobserver reproducibility were assessed using intraclass correlation coefficients. The correlation between SBRI and SVRI was analyzed using Pearson correlation coefficients. All statistical analyses were performed using SPSS (version 22.0; SPSS Inc., Chicago, IL, USA), and a *P* value of <0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

Thirty-six septic patients were enrolled in this study. Their mean age was 63.7 ± 20.4 years, and 69.4% were male (Table 1). Thirty-three (91.6%) of the patients had underlying diseases, including neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, immunologic, metabolic, and neoplastic diseases. The mean APACHE II score was 23.3 ± 7.9. Respiratory infections were the most common (83.3%) type of infection. The overall culture positive rate was 63.8%, and gram-negative pathogens were the most common (50%). The most commonly used vasoactive agent was norepinephrine (83.3%).

3.2. Ultrasound measurements

3.2.1. Incidence angle of the ultrasound beam

The incidence angles of the ultrasound beam at the four points were 23.9 ± 11.1° (right SB, 1 cm depth); 7.4 ± 8° (right SB, 1.5 cm depth); 23.3 ± 11.7° (left SB, 1 cm depth), and 6.5 ± 7.4° (left SB, 1.5 cm depth) (Table 2).

Table 1
Demographics of 36 septic patients admitted to the medical intensive care unit.

Variables	$N = 36$
Age (years)	63.7 ± 20.4
Sex (male), n (%)	25 (69.4)
Underlying diseases, n (%)	33 (91.6)
APACHE II score	23.3 ± 7.9
Site of infection, n (%)	
Central nervous system	1 (2.7)
Bacteremia	14 (38.8)
Respiratory	30 (83.3)
Genitourinary	5 (13.8)
Abdominal	4 (11.1)
Wound/soft tissue	1 (2.7)
Multiple-site infection (≧2)	11 (30.5)
Culture positive, n (%)	23 (63.8)
Pathogen, n (%)	
Gram positive	5 (13.8)
Gram negative	18 (50)
Fungus	2 (5.5)
Virus	1 (2.7)
Unknown	13 (36.1)
Vasoactive-inotropic agents used, n (%)	
Dopamine	7 (19.4)
Norepinephrine	30 (83.3)
Dobutamine	3 (8.3)
Multiple agents (≧2)	8 (22.2)
Cardiac characteristics	
Heart rate (bpm)	134.4 ± 35.6
Systolic blood pressure, mm Hg	121.5 ± 10
Diastolic blood pressure, mm Hg	61.2 ± 13.6
Mean arterial pressure, mm Hg	80.2 ± 15.7
Central venous pressure, mm Hg	10.5 ± 4.5
CI, L/min/m2	3.2 ± 1.1
SVRI, dyn*s*cm^{-5}*m^2	1977 ± 706.5
Laboratory data	
Lactate, mg/dL	30.9 ± 36.6
Artery pH	7.36 ± 0.2
Artery HCO3$^-$, mmol/L	21.5 ± 8.3

APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = cardiac index; SVRI = systemic vascular resistance index.

3.2.2. Correlation of SVRI and Doppler SBRI

Correlations between SVRI and different depths of SBRI in the 36 patients are shown in Table 2, and included 96 patient days and 951 ultrasound measurements. Significant positive correlations at the four points were noted in overall measurements, including the first, second, and third measurements ($p < .05$). In particular, the correlation coefficients were all higher than 0.87 ($p < .001$).

It was difficult to assess all of the SBRI points in all of the patients due to wounds or when they could not be identified by ultrasound. Fig. 2 shows the positive correlations between three simultaneous SVRI measurements and different SBRI points, all of which showed good correlations in first, second and third measurements ($p < .001$).

Table 2
Correlation between SBRI and SVRI over four points in the 36 patients.

Points of measurements	Results of measurements	r	p-Value
Right hand (1 cm), average 23.9°	First measurement	0.897	<0.001*
	Second measurement	0.911	<0.001*
	Third measurement	0.904	<0.001*
Right hand (1.5 cm), average 7.3°	First measurement	0.908	<0.001*
	Second measurement	0.902	<0.001*
	Third measurement	0.896	<0.001*
Left hand (1 cm), average 23.2°	First measurement	0.886	<0.001*
	Second measurement	0.881	<0.001*
	Third measurement	0.883	<0.001*
Left hand (1.5 cm), average 6.5°	First measurement	0.896	<0.001*
	Second measurement	0.873	<0.001*
	Third measurement	0.895	<0.001*

r = correlation coefficient; SVRI = systemic vascular resistance index; SBRI = snuffbox resistive index.

* *p* value <.05; statistically significant.

When analyzing the Doppler waveforms of the radial artery in the SB, a higher SVRI was correlated with sharp waveforms. Reversed diastolic flow was detected when the SVRI was particularly high and the SBRI value exceeded 1.00 (Fig. 3A). In contrast, a lower SVRI was correlated with smooth waveforms and lower SBRI values (Fig. 3B). Compared with a normal range of SVRI (1700–2400 dyn*s*cm^{-5}*m^2) as measured by the PiCCO system [20], an SVRI of 1700 dyn*s*cm^{-5}*m^2 was approximately equal to an SBRI of 0.97, and 2400 dyn*s*cm^{-5}*m^2 was approximately equal to an SBRI of 1.1 (Fig. 2).

3.2.3. Repeatability and reproducibility

The correlation coefficient of interobserver reproducibility of the SBRI was 0.962 (0.684–0.996). Similarly, the correlation coefficients of intraobserver repeatability of the RI at 1 cm depth of the right SB, 1.5 cm depth of the right SB, 1 cm depth of the left SB, and 1,5 cm depth of the left SB were 0.962 (0.945–0.974), 0.975 (0.965–0.983), 0.982 (0.974–0.988), and 0.985 (0.978–0.99), respectively. All correlation coefficients were above 0.75, which indicated good agreement [21].

4. Discussion

In this prospective study, we demonstrated a strong correlation between Doppler SBRI and SVRI as measured by TPID in septic patients. This technique is a non-invasive method to monitor systemic vascular resistance (SVR), and it can be used to guide treatment in septic patients. Bedside ultrasound is a feasible tool and easy to perform, and it can shorten dynamic investigations, and reduce the risk of catheter infections and perfusion-related complications in septic patients.

Our results are similar to the study by Ban et al. [14], in which SBRI was well correlated with SVRI in patients who received cardiac surgery. However, the pathophysiology of septic patients involves endothelial injury and vasodilatation of peripheral resistance vessels, and the vasodilation of vessels may be not uniform across tissue beds throughout the whole body [10,22,23]. Therefore, measuring the vascular resistive index at one position may not represent systemic vascular resistance in septic patients. However, we demonstrated a good correlation between SBRI and SVRI in our septic patients. The average correlation coefficients were about 0.9 in our study, which is better than the 0.8 reported by Ban et al. [14], which may be because we compared the mean of three repeated SBRI measurements with SVRI, thereby increasing the reliability [24].

The analysis of ultrasonic waveforms is important and can be affected by the incidence angle (ultrasound beam and blood flow direction). The error of measured waveforms can be reduced to <20% if the incidence angle is <60°, which means that the smaller the incidence angle, the smaller the error of the detected waveforms, resulting in a more precise resistive index [14]. The radial artery in the SB is a peripheral vessel that provides the smallest incidence angle for ultrasound. We evaluated two different depths for each radial artery in the SB due to difficulties in making the measurements. The shallow position (1 cm) was easier to identify but had a larger incidence angle, whereas the deeper position (1.5 cm) was more difficult to identify but had a smaller incidence angle. However, the results at the different depths in the same radial artery in the SB were well correlated with SVRI, as both of the incidence angles were <30°.

Peripheral arteries often show a triphasic flow containing forward systolic flow (first phase) followed by early diastolic reversed flow (second phase), and reduced forward flow in diastole (third phase) [25]. When warm shock develops, warm skin indicates vasodilation. We found that the SVR was lower when the waveforms rarely detected the second phase (early diastolic reversed flow) of SBRI (Fig. 3B), indicating vasoplegia [10,21,22,25]. Vaso-active agents should be titrated immediately to increase the SVR to improve peripheral perfusion [10,26,27]. When cold shock developed, a higher SVR and low CI were noted. If the SVR increased too much, the waveforms showed decreased diastolic flow and reversed end-diastolic flow (Fig. 3A), which could

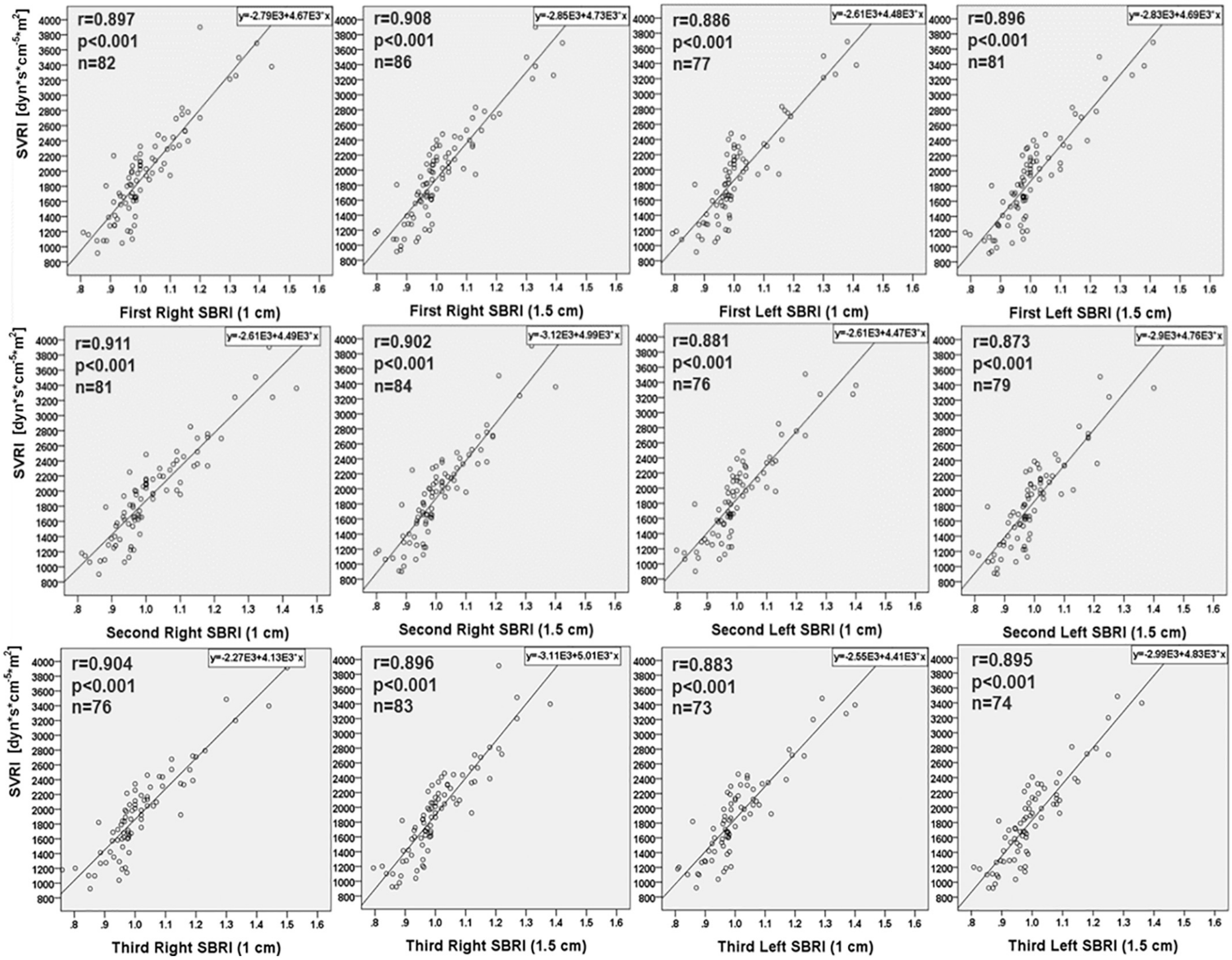

Fig. 2. Correlation between resistive index of three measurements at different depths of snuffbox resistive index (SBRI) and simultaneous systemic vascular resistance index (SVRI) (dyn*s*cm^{-5}*m^2).

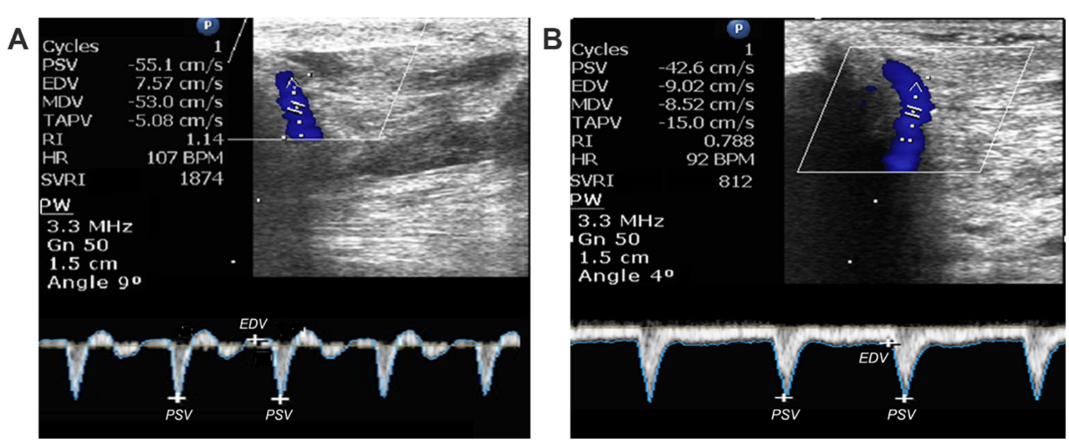

Fig. 3. The Doppler waveforms of the radial artery in the snuffbox (SB). (A) High snuffbox resistive index (SBRI): Doppler waveforms with reversed diastolic flow at the SB (systemic vascular resistance index (SVRI) = 1874; resistive index (RI) = 1.14). (B) Low SBRI: Doppler waveforms without reversed diastolic flow at the SB (SVRI = 812; RI = 0.788). PSV = peak systolic velocity, EDV = end-diastole velocity.

result in transient ischemic damage of peripheral perfusion [14]. In such cases, vasodilatory and inotropic medications (such as dobutamine and milrinone) should be administered to loosen the arteries and increase flow in the diastolic phase.

The limitations of this study include the small sample size and the prospective design conducted at a single center. Therefore, there is a risk of information bias. In addition, we only performed measurements on the radial artery in the SB, and other peripheral arteries may not have the same correlations. Future studies comparing RI in different arteries with SVRI are warranted.

5. Conclusion

We demonstrated a strong correlation between Doppler SBRI and SVRI as measured by TPID in septic patients. SBRI measured by ultrasound had good repeatability and reproducibility. In addition, SBRI can be used to evaluate peripheral circulatory disturbances in septic patients.

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Availability of data and materials

Not applicable.

Authors' contributions

EPL and SHH conceived and designed the study. SHH and HPW participated in data analysis. OWC, CYL, YTS and IMH gathered the data. EPL, SHH and JJL drafted the manuscript, with all authors revising it critically for intellectual content. All authors have read and approved the final version of this manuscript.

Competing interests

None.

Consent for publication

All authors have reviewed and approved the manuscript for publication.

Ethics approval and consent to participate

The study protocol was approved by the Institution Review Board and Ethics Committee of Chang-Gung Memorial Hospital, Taiwan (IRB No.: 201700739A3).

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