Pakistan Journal of Intensive Care Medicine
eISSN: 2708-2261; pISSN: 2958-4728
www.pjicm.com
DOI: https://doi.org/10.54112/pjicm.v4i01.27
Pak. J. Inten. Care Med., volume 2024: 27

Original Research Article

IMPACT OF NOREPINEPHRINE DOSAGE INCREASE AND VOLUME EXPANSION ON CAPILLARY REFILL TIME IN SEPTIC SHOCK PATIENTS

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(Received, 05th February 2024, Revised 28th February 2024, Accepted 10th March 2023, Published 20th March 2024)

ABSTRACT

Background: *When evaluating patients with acute circulatory failure, one clinical feature that may be quickly determined at the bedside is the capillary refill time (CRT).**Objective:*** *The objective of this observational study was to describe the changes in CRT that occur as a result of volume expansion and increased dosages of norepinephrine, along with related macro-circulatory variables, in patients suffering from septic shock. Study **Design:*** *This was an observational study. **Setting:*** *The study was conducted at Bahria Town International Hospital Lahore and Services Institute of Medical Sciences. **Duration of Study:*** *The study was conducted over six months from January 2, 2023, to July 30, 2023. **Methods:*** *We measured mean arterial pressure (MAP), cardiac index (CI), and five consecutive CRT readings in 40 septic shock patients. These measurements were taken before and after a 500 mL saline infusion in 20 patients and before and after an increase in norepinephrine dosage in another 20 patients. **Results:*** *The "norepinephrine" group had lower SAPS II and SOFA scores than the "volume expansion" group. When all patients were assessed together, volume expansion significantly lowered heart rate while increasing MAP, diastolic arterial pressure, CI, CVP, and CRT. Fluid-induced increases in CI of ≥ 15% were observed in 11 patients (55%). In fluid responders, fluid infusion significantly raised MAP by 31% (11-49%) and CI by 26% (20-42%). Increased norepinephrine levels may lower CRT in patients with a baseline value of fewer than 3 seconds. Increasing norepinephrine has a low possibility of decreasing CRT in patients with baseline CRT ≥ 3 seconds if the MAP increase is <15%. However, the decrease in CRT is inconsistent in patients with baseline CRT ≥ 3 seconds when norepinephrine increases MAP by ≥ 15%. Univariate regression analysis revealed a correlation between the absolute value of CRT and lactate levels, heart rate, norepinephrine dosage, gender, SAPS II, and ICU mortality. In a multivariate analysis that included all physiological parameters with a p-value <0.1 in univariate linear regression, only lactate upon admission had a significant association with the absolute value of CRT. **Conclusion:*** *CRT uncommonly improves with therapy in individuals with septic shock and prolonged CRT when volume expansion raises cardiac output by <15% and increasing the dosage of norepinephrine increases MAP by <15%. CRT's response varies when there are significant effects of fluid infusion on cardiac output and norepinephrine on MAP; in some patients, it decreases while remaining consistent in others. CRT functions as an indicator of microcirculation in this context.*

Keywords: Capillary Refill Time, Cardiac Output, Critical Care, Norepinephrine, Septic Shock, Volume Expansion

INTRODUCTION

Capillary refill time (CRT) is one clinical parameter that may be easily measured at the bedside when assessing individuals with acute circulatory failure. (1). Extended CRT has been linked to a higher death rate in individuals suffering from cardiogenic shock. (2) or septic shock(3). The ANDROMEDA-SHOCK research highlighted the interest in CRT, which showed that resuscitation targeted at either normalising CRT or maintaining or lowering lactate levels within an 8-hour intervention phase had a comparable impact on 28-day mortality among individuals with septic shock (4).

CRT is increasingly regarded as a vital monitoring element for resuscitating patients in septic shock (5), especially in environments with limited resources (6). Restoring organ perfusion in an individual experiencing septic shock is the goal of resuscitation. (7). Consequently, observing variations in CRT regularly may be utilised to determine the perfusion state(8)

The physiological factors that influence CRT are not well understood yet. Skin perfusion and vascular reactivity are reflected in CRT (9). Thus, it ought to be impacted by the nature and functioning of the microcirculation as well as by a few macrocirculatory factors, including cardiac output and mean arterial pressure (MAP). According to a recent systematic review, there is an inverse relationship between MAP and CRT. (10)However, a thorough study has not been conducted on how fluid infusion and norepinephrine, the two major therapies for septic shock, affect CRT.

Therefore, the observational research conducted in septic shock patients aimed to characterise the alterations in CRT with volume expansion and an increase in norepinephrine dosage, together with associated macro circulatory parameters.

METHODOLOGY

This prospective investigation was carried out at Bahria Town International Hospital Lahore**,** from January 2, 2023, to July 30, 2023. The hospital's ethics committee gave its approval for this research. It was carried out in compliance with STROBE criteria. Patients or their relatives gave informed consent.

The requirements for inclusion were (i) being at least eighteen years old and (ii) having septic shock as defined by the present definition (11), (iii) If instructed by the attending doctors, volume expansion or raise the dosage of norepinephrine. Being pregnant, extracorporeal membrane oxygenation, dark skin, and previous episodes of the Raynaud phenomenon were the exclusion criteria. Volume expansion was usually decided upon when there were indications of reduced

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urine production, increased lactate or carbon dioxide-derived indicators, mottling, or elevated CRT. The targeted MAP was used to determine when to increase norepinephrine dosage.

CRT assessment was taken at the correct index's palmar surface, utilising a standardised technique that has been previously discussed. Pressure was delivered to the finger via the piston using a 10-mL syringe. The syringe's port was blocked, and 10 mL of air was inserted. Standardising the pressure at the fingertip was achieved by compressing the syringe's air capacity from 10 to 7 mL for 7 seconds. In less than three minutes, five CRT readings were taken at each hemodynamic state.

Transpulmonary thermodilution was used for measuring CI. This involved inserting three 15-mL cold boluses of normal saline via the central venous catheter and computing their average. As needed, patients were equipped with an internal jugular vein catheterization and an arterial femoral catheter tipped with a sensor. CVP recordings were done. A fluid-caused rise in CI of at least 15% was used to indicate responsiveness to fluids.

Every patient's baseline hemodynamic variables were evaluated. Participants in the "volume expansion group" received an intravenous 500 mL entire bolus of NaCl 0.9% for 15 minutes. The "norepinephrine group" patients had their dose of the drug raised at the discretion of the medical specialist. The same variables that were measured before the intervention were determined in the "volume expansion group" immediately following the end of the fluid injection and in the "norepinephrine group" following the stabilisation of MAP (i.e., variation < 15% of MAP), even in cases where the MAP level achieved surpassed the original MAP target. Measurements of arterial lactate were only made before the interventions. Quantitative variables were compared across patient groups using the Mann-Whitney U statistic and between study periods using the Wilcoxon matched-pairs analysis. The quantitative variables were provided as median [interquartile range]. We determined the coefficient of variation (CV) of the CRT for each subject. The CRT's determinants and variations were examined using regression linear analysis. P-values were regarded as statistically significant if they were less than 0.05.

RESULTS

Table 1 summarises the baseline parameters of the 40 enrolled patients. The "norepinephrine" group had lower SAPS II and SOFA scores than the "volume expansion" group, whereas other variables were comparable.

When all patients were assessed combined, volume expansion significantly lowered heart rate while increasing MAP, diastolic arterial pressure, CI, CVP, and CRT. Fluid-induced increases in CI of ≥ 15% were found in 11 individuals (55%). In fluid responders, Fluid infusion substantially raised MAP by 31 (11-49%) and CI by 26 (20-42%).

Fluid infusion did not affect CRT in patients having a baseline CRT of less than 3 s. Except for one fluid non-responder with a baseline CRT of ≥ 3 s, the CRT remained unaffected. One fluid non-responder having a baseline CRT of > 3 s had a substantial drop in CRT from 13.8 to 8.7 s.

Increased norepinephrine levels may lower CRT in patients with a baseline value of fewer than 3 seconds. Increasing norepinephrine has a low possibility of decreasing CRT in patients with baseline CRT ≥ 3 s if the MAP shift is < 15%. However, the drop in CRT is inconsistent in patients with baseline CRT ≥ 3 s when norepinephrine raises MAP by > 15%.

Fluid responders having a baseline CRT of 3 s or higher had an average reduction in CRT. In 5 patients, it reduced by more than 23%, whereas in 3 individuals, it stayed constant. It dropped by ≥ 23% in two individuals. The period from the beginning of septic shock to fluid infusion did not vary between the two groups (8 [4-416] hours vs. 172 [25-261] hours, correspondingly, p = 0.27).

Univariate regression study revealed a correlation between the absolute value of CRT and lactate, heartbeat, norepinephrine dosage, gender, SAPS II, and ICU mortality. In a multivariate study that included all physiological parameters with a p-value < 0.1 in univariate linear regression, only lactate upon admission had a significant association with the absolute value of CRT.

Table 1: Patient features at enrollment and ICU mortality.

Variable	Volume expansion group N=20	Norepinephrine group N=20	P-value
Age – years	68 [56–79]	67 [60–75]	0.32
Male sex – no (%)	12 (60)	14(70)	0.41
BMI – kg/m2	26 [21–33]	28 [26–34]	0.82
SAPS II	55 [50–62]	49 [39–58]	0.01
SOFA	11 [9–14]	9 [8–12]	0.01
Ischemic heart disease	13 (65)	14(70)	0.23
Chronic kidney disease	6(30)	8(40)	0.12
Diabetes mellitus	11(55)	10(50)	0.63
Hypertension	7(35)	4(20)	0.54
Arterial lactate – mmol/L	3.9 [2.4–4.9]	2.3 [1.9–3.2]	0.001
Source of infection – no (%)			
Pneumonia	13(65)	9(45)	0.89
Abdominal infection	3(15)	5(25)	0.96
Urinary tract infection	2(10)	4(20)	0.65
Catheter-related infection	1(5)	1(5)	0.43
Others	1 (5)	1(5)	0.55
Mechanical ventilation	17(85)	18(90)	0.61
ICU mortality – no (%)	9 (45)	7(35)	0.48

Table 2: Effects of volume expansion and the increase in norepinephrine dose on hemodynamic variables

Variable	Before intervention	After intervention	P value
Volume expansion			
MAP–mmHg	71 [63–80	83 [76–102]	< 0.0001
DAP–mmHg	54 [48–63	63 [57–74]	0.004

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CVP–mmHg	8 [5–10	11 [8–13	< 0.0001
CI–L/min/m2	2.58 [2.08–3.08]	2.96 [2.34–3.58]	0.0002
HR–beats/min	107 [87–119]	104 [82–116]	0.03
Arterial lactate–mmol/L	3.9 [2.4–4.9]	-----	
Norepinephrine			
Rate–µg/kg/min	0.75 [0.29–1.68]		
Delay between initiation and CRT–hour	22 [9–34]	--	
CRT–sec	5.28 [3.34–7.54]	4.28 [2.87–5.99]	< 0.0001
Increase in nor epinephrine dose			
MAP–mmHg	67[61–76]	86 [81–104]	< 0.0002
DAP–mmHg	51 [46–61]	63 [57–77]	< 0.0001
CVP–mmHg	10 [8–14]	13 [9–15]	0.052
CI–L/min/m2	2.98 [2.34–3.66]	2.97 [2.41–3.96]	< 0.0001
HR–beats/min	88 [74–104]	88 [73–99]	0.63
Arterial lactate–mmol/L	2.4 [2.1–3.3]		
Norepinephrine			
Rate–µg/kg/min	0.24 [0.09–0.52]	0.44 [0.32–0.76	< 0.0002
Delay between initiation and CRT–hour	59 [16–198		
CRT–sec	2.74 [1.64–4.91	2.36 [1.32–4.24]	0.008

Table 3: changes in hemodynamic parameters in fluid responders after volume expansion

Variable	Before VE	After VE	P value
Fluid responders N=11			
MAP–mmHg	69 [62–78]	84 [79–105]	< 0.0001
DAP–mmHg	54 [48–59]	65 [57–71]	0.0002
CVP–mmHg	7 [5–10]	10 [6–13]	0.003
CI–L/min/m2	2.44 [1.79–3.16]	3.27 [2.38–4.13]	< 0.0001
HR–beats/min	113 [73–117]	108 [77–117]	0.40
Arterial lactate–mmol/L	2.9 [2.1–4.7]	-----	
Norepinephrine			
Rate–µg/kg/min	0.57 [0.29–1.43]	0.57 [0.29–1.43]	
Delay between initiation and CRT–hour	19[5–26]	--	
CRT–sec	5.59 [3.12–7.67]	3.52 [2.41–4.81]	< 0.0001

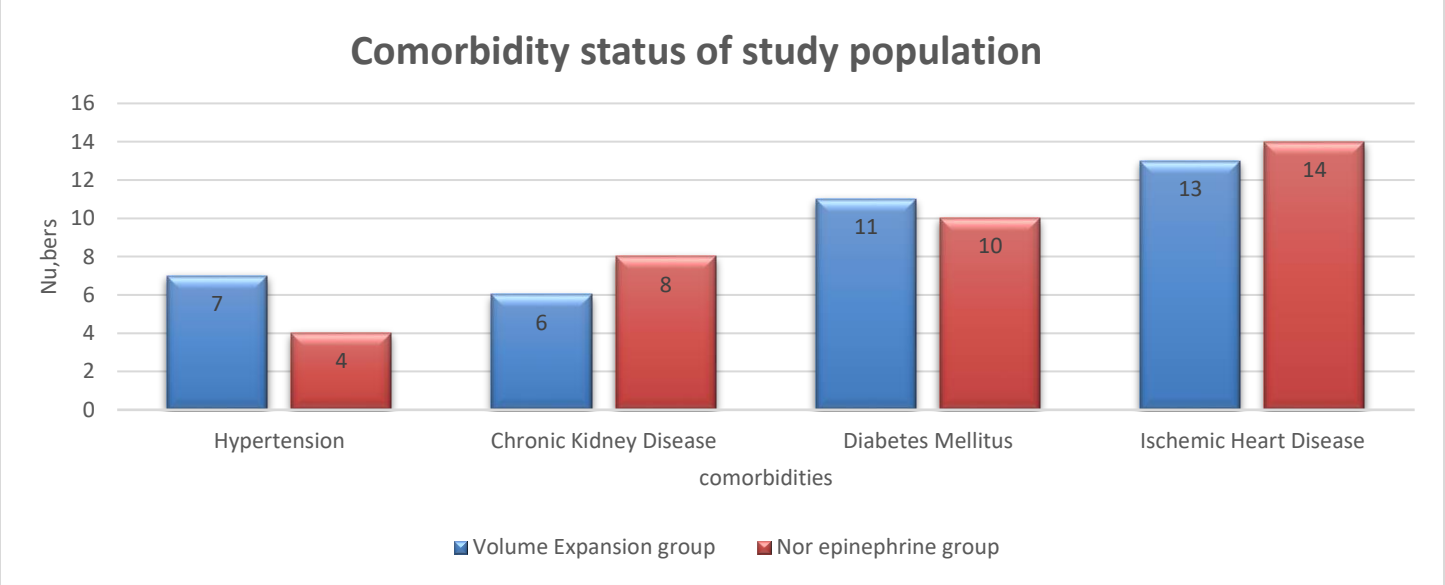

Fig 1 shows the status of the study population about comorbidities.

DISCUSSION

The results of our study on septic shock patients found that fluid infusion has no impact on CRT if the baseline value is less than 3 s. In fluid responders having a baseline CRT ≥ 3 s, CRT drops in some patients but remains constant in others. Increased norepinephrine levels may lower CRT in patients with a baseline value of fewer than 3 seconds. Increasing norepinephrine has a low possibility of decreasing CRT in patients with baseline CRT ≥ 3 s if the MAP shift is < 15%. However, the drop in CRT is inconsistent in patients with baseline CRT ≥ 3 s when norepinephrine raises MAP by > 15%.

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In severely sick patients, CRT is a valuable technique to measure tissue perfusion. (8). The ANDROM-EDA-SHOCK research in patients with septic shock found that CRT-targeted resuscitation was not significantly different from lactate-targeted resuscitation in terms of 28-day mortality. However, it resulted in fewer organ dysfunctions at 72 hours and decreased mortality among those with fewer at baseline. (12). The study recommends monitoring CRT changes to track tissue perfusion during sepsis.

Fluid infusion resulted in unaltered CRT in all but one individual having a baseline CRT of less than 3 s. This demonstrates that CRT represents tissue perfusion, which should stay constant with fluids if normal. In fluid non-responders, CRT did not change in all but one case. A fluid bolus may not appreciably enhance tissue perfusion if cardiac output remains unchanged. The advantageous rheologic impact of volume expansion may explain why the only fluid non-responder's CRT improved after fluid administration. (13).

Fluid responders with a prolonged CRT at baseline experienced varying responses, with some patients experiencing a shortening and others staying unchanged. This shows that a considerable increase in cardiac output may not always result in improved tissue perfusion. This can be answered by the fact that the dissociation of macro and microcirculatory variables in septic shock patients has been widely recognized (14). Our findings suggest that the macro-microcirculation interaction persists during the early stages of septic shock (14).

For the most part, the CRT response to norepinephrine administration was comparable to how it responded to the fluid bolus, i.e. people having baseline CRT < 3 s showed no change in CRT in general. As far as we know, no research has been done on CRT's response to norepinephrine. First, of all the individuals in which the norepinephrine dosage was increased, just a single patient's CRT raised, implying that the drug's vasoconstrictive action does not generally impact CRT. Secondly, if MAP increased a little, as with fluid bolus, a slight improvement in CRT could be anticipated in individuals with long baseline CRT. Like fluid, the CRT response varied, showing a dissociation between MAP and CRT changes in specific individuals, where baseline CRT was > 3 s while MAP increased ≥ 15%. Once more, if it is agreed that the characteristics of the microcirculation influence CRT to some extent (15). This is consistent with research showing a wide range of microvascular reactions regarding norepinephrine dosage variations (16). This is also in line with a prior study that found no correlation between raising the MAP desired level and changes in mottling, another indicator of skin perfusion (17).

However, this interpretation needs to be used with caution. A small number of cases were seen in each subgroup initially. Second, MAP changes were categorised near the predetermined 15% threshold. Third, the exact reason for how the behaviour of CRT shifts during norepinephrine changes cannot be determined, and it's probable that the simultaneous vasoconstriction countered the impact of the MAP increase. We tried to identify the variables that would explain the CRT absolute value using univariate and multivariate evaluations. Our findings that arterial lactate levels and CRT were related were in line with previous research. (18). Even though cutaneous blood flow is associated with CRT (9).

Our study has many limitations. One is the small sample size, which is why these results cannot be generalized. Another is that we did not examine cutaneous blood flow or microcirculation, which may have enabled us to more thoroughly examine all possible CRT determinants. Third, we did not evaluate how variations in norepinephrine dosage and fluid infusion affected tissue oxygenation parameters. Fourth, the majority of our patients had their MAP recovered at baseline because we didn't involve patients who were in the very early stages of septic shock.

CONCLUSION

CRT uncommonly improves with therapy in individuals with septic shock and prolonged CRT when volume expansion raises cardiac output <15% and increasing the dosage of norepinephrine increases mean arterial pressure (MAP < 15%), CRT's reaction dissociates when there are significant effects of fluid infusion on cardiac output and norepinephrine on MAP, in particular people it decreases while remaining consistent in others. CRT functions as an indicator of microcirculation in this regard.

DECLARATIONS

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned.

Consent for publication

Approved

Funding

Not applicable

CONFLICT OF INTEREST

The authors declared absence of conflict of interest.

AUTHOR CONTRIBUTION

RIZWAN PERVAIZ
Study Design, Review of Literature.
Conception of Study, Development of Research Methodology Design, Study Design,, Review of manuscript, final approval of manuscript.
BUSHRA ARIF
Conception of Study, Final approval of manuscript.
Manuscript revisions, critical input.
HASSAN AHMED
Coordination of collaborative efforts.
Data acquisition, analysis.
SABA ZARTASH BUKHARI
Manuscript drafting.
Data entry and Data analysis, drafting article.
LAILA HASSAN ISSA
Study Design, Review of Literature.
Manuscript revisions, critical input.
SITARA RAZA
Coordination of collaborative efforts.

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