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A Novel Approach: Non Invasive Management of Patients under the Surviving Sepsis Campaign Guidelines: A Case Series of 5 Patients.

Piyush N Mallick,[1] Surjya P Upadhyay,[2] Manish Jagia,[1] Osman Pamkar,[1] Koppolu Y Prasad[3]
1.Senior Registrar, 2. Registrar, 3. Senior Consultant
Al Jahra Hospital, Kuwait

Corresponding Author: Dr. Piyush N Mallick, MD, Post box-2921 Postal code 22030, Salmiya, Kuwait. Phone: +965-97594905 Email- piyush_mallick@hotmail.com

About the Author: Piyush Mallick did his graduation from VSS Medical college Orissa in 1995 followed by post graduation in Anaesthesiology from All India Institute of Medical Sciences, Delhi in 1998. He worked as Assistant Professor in the same institute from August 2002 to June 2004. Presently, he is working at Al Jahra Hospital, MOH, State of Kuwait since June 2006. His areas of interests are: Anaesthesia for bariatric surgery, TIVA, Paediatric Anaesthesia, Critical Care, Trauma, Ultrasonography & Echocardiography in Anaesthesia and Critical Care

Abstract: Fluid resuscitation is the most critical intervention during initial phase of management in septic patients. Traditional approach for fluid management relied on invasive line for volume estimation and response to therapy which are complicated techniques and sometime inaccessible or contraindicated in certain patients. We describe some simple non invasive methods which can be followed easily for estimation of fluid status and response to fluid therapy. We present a case series of five patients where we successfully used non invasive techniques of fluid assessment and response to fluid therapy. We used ultrasonography of IVC (inferior venacaval assessment) and Echocardiography evaluation of velocity time integral through aortic valve flow (VTI) to guide fluid administration as surrogate markers of CVP. Periodic estimation of lactate concentration to assess tissue oxygenation with aim of lactate reversal of 10% per hour (equivalent to central venous oxygen saturation of 70%) was used in place of central venous oxygen saturation to guide appropriate therapy. Similarly, although early intubation is recommended in managing septic patients there might be a role of non invasive ventilation in selected patients as reflected in our cases. All our cases were managed without endotracheal intubation as well. Successful outcome of all five of our cases may indicate there might be a near total non invasive way to manage cases of severe sepsis and septic shock.

Keywords: Sepsis, fluid resuscitation, ultasonography, caval index, echocardiography, lactate reversal.

Background: Surviving sepsis campaign guideline in the management of sepsis recommends placement of invasive line in early goal directed therapy (EGDT) to maintain a CVP at 8 and 12 cmH_2O in nonventilated and ventilated patients respectively, mean arterial blood pressure of more than 65 mmHg, urine out put more than 0.5ml/kg/hr and mixed venous saturation or a central venous saturation of 65% or 70% respectively, which are critical for successful outcome.[1]

Placement of invasive line is sometimes difficult or inaccessible or contraindicated in certain situations and it also has its own risks and disadvantages. We tried to incorporate some standard non-invasive techniques such inferior vena cava (IVC) diameter and collapsibility (caval index) using ultrasound[2-7], velocity time integral (VTI) through aortic valve using echocardiography,[8-12] lactate reversal per hour to guide fluid therapy and to maintain EGDT. We were able to achieve goal of EGDT in these 5 patients of severe sepsis with septic shock using non-invasive techniques with lactate reversal as the surrogate marker of central venous oxygen saturation. Non-invasive ventilation was used in all patients with successful outcome. Aim of this presentation is to convey massage to healthcare professional team that non-invasive techniques can be easily incorporated in the management of septic patients especially when invasive techniques are inaccessible or contraindicated.

Patients and Methods: Method used in these patients were inferior vena cava (IVC) assessment, transthoracic echocardiography guided velocity time integral (ECHO VTI) blood flow through aortic root which were used to assess volume status and response to fluid loading. Lactate reversal of 10% was considered as equivalent to mixed venous oxygen saturation (SVO_2) of 70%. Interestingly all patients were managed with non invasive ventilation too.

Inferior Vena cava Assessment: Tran abdominal approach for assessment of IVC with standard size Ultrasound probe was used for both 2D and M mode. First of all aorta was identified by placing the probe in longitudinal plane, midline in epigastric region just below the xiphi-sternum. Once aortic pulsation was confirmed, probe was slided to right to visualize IVC. IVC diameter as during inspiration and expiration was noted at 4 cm below the right atrium. Caval index was calculated as (maximum diameter–minimum diameter) X 100/maximum diameter. Maximum IVC diameter of more than 2 cm with caval index less than 30% was considered as CVP value of 10 cmH_2O or more and caval index of more than 50% irrespective of diameter was consider as CVP of less than 5 cm H_2O respectively. (Image 1: Showing collapsibility of IVC and response after fluid challenge).

ECHO VTI: Transthoracic Echocardiographic evaluation of Velocity Time Integral (ECHO VTI) of flow through aortic valve was used to assess and measure the response to fluid challenge. Long axis 5 chambers view with M mode was used to assess the flow through the aortic valve. Peak velocity of flow (Vpeak) through the aortic valve was used as VTI value. Percentage of change in VTI value was calculated as - Maximum VTI value (Vpeak max)-minimum VTI (Vpeak min)/mean VTI or V peak mean. More than 12% change in VTI value with respiration was consider as fluid responsive as suggested by Feissel et al[9] and fluid resuscitation was continued till the VTI variation was less than 12%. (Image 2 and image 3 showing the echo images of flow through aortic root).

Percentage decline in lactate level was used to represent central venous oxygen saturation (SVO_2), > 10% decline in lactate level per hour was considered as SVO_2 of 70%. Persistent high lactate was treated using SSC guideline in the form of fluid, Blood transfusion or Dobutamine, depending upon the clinical situations. Arterial line was used for lactate measurement as our BGA machine was calibrated for lactate, and lactate was measure along with BGA values.

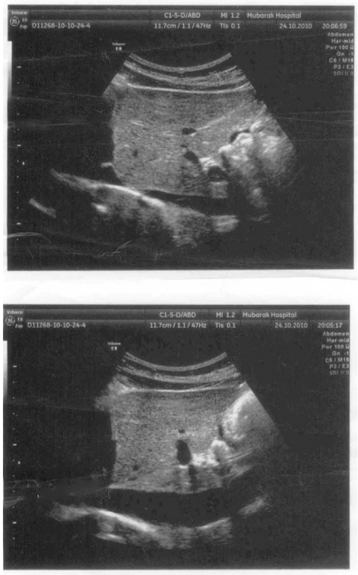

Image 1: Ultrasonographic Images of IVC before and after fluid resuscitation

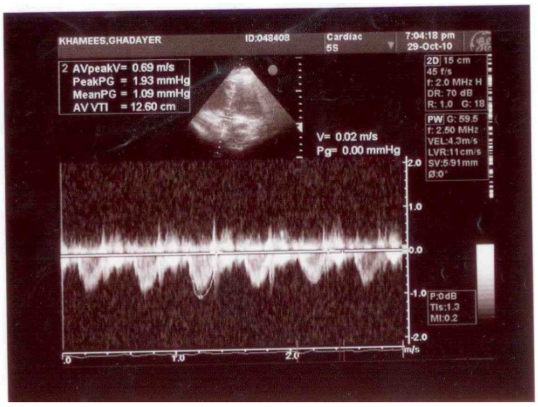

Image 2: Echo VTI trace through LVOT before fluid resuscitation

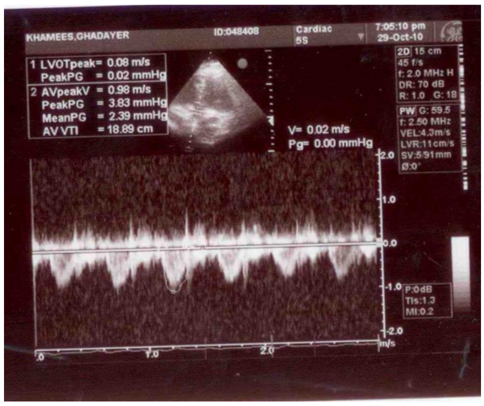

Image 3: Echo VTI trace through LVOT after fluid resuscitation

Ventilation: Non-invasive ventilation in the form of BiPAP with inspiratory pressure of 14 cm H_2O and expiratory 8 cm H_2O was used. Our aim was to continue BiPAP till the patients remained to be conscious with intact airway reflexes and respiratory parameters continued to improve.

The different case scenario we encounter is described briefly as follows:

Case 1: A 22-year-old female with fever for 3 days and lower abdominal pain was brought to the emergency room. Initial parameters: blood pressure 60/40 mmHg, heart rate 120/min respiratory rate 25/min and oxygen saturation of 90%. Blood Gas Analysis (BGA) showed severe metabolic acidosis with PH 7.10, HCO_3 18, base excess (BE) of - 9, PO_2 10 KPa with 10 litres oxygen via face mask and PCO_2 was 3.8 KPa and Lactate 5.2 mmol/l. Her prothrombin time was prolonged with INR of 2.8, so placement of invasive line was deferred. Initial fluid resuscitation was done with 2 litres of Lactated Ringer solution infused over 1 hour. However, despite aggressive fluid resuscitation her blood pressure did not improve. Transabdominal Ultrasonography and transthoracic ECHO VTI were used to estimate the volume status of the patient. Inferior vena cava (IVC) revealed a maximum diameter of 1.8 cm on ultrasonography with more than 50% collapse with respiration. ECHO VTI showed more than 25% variation with respiration. Aggressive fluid therapy continued targeting IVC diameter of more than 2 cm with less than 30% collapse with respiration and VTI variability of less than 12%. After receiving around 4 litres of crystalloid over 2 hrs with norepinephrine of 10 mcg/min, her systolic blood pressure came above 90 mmHg. A patient was transferred to ICU after initial stabilization while continuing fluid resuscitation. Three hours later, IVC collapsibility was decreased to less than 30% and the maximum diameter became 2.2 cm with ECHO VTI absolute value of 30 with respiratory variation of less than 10%. By the time mean arterial blood pressure of 70mmHg was achieved. Computed Tomography (CT) abdomen revealed a large tubo-ovarian mass with pelvic collection accompanying free fluid suggestive of pelvic abscess. Urgent Laparotomy with drainage of abscess was done with a lower abdominal incision. Intraoperative course was uneventful. Patient was extubated on BiPAP in ICU. Rest of the management was done as per SSC guideline. Patient's condition gradually improved with normal BGA value and weaned successfully from non-invasive ventilation after 24 hrs. Patients was shifted from the ICU after 48 hrs and discharged from hospital on 7^{th} day without any sequel.

Case 2: A 54-year diabetic female shifted to ICU for persisting hypotension and oliguria for 2 hrs, history revealed high grade fever associated with headache and neck stiffness, productive cough and generalized rashes all over body for 2 days. On examination patients was conscious but looked exhausted, febrile with temperature of 39^0C, respiratory rate 30 per min, heart rate 125 per min, blood pressure 70/50 mmHg, and general purpuric rashes all over the body. Her laboratory results revealed total leucocytes count (TLC) of 25000/cc, platelets count of 30,000/cc, INR of 3. BGA showed severe metabolic acidosis with PH of 7.15, PO_2 of 8.9 KPa, PCO_2 of 3.9 KPa, BE of -12 and lactate of 4.4 mmol/lit. Impression of pneumococcal meningitis with septic shock was kept as differential diagnosis. CVP line was not inserted because of obvious coagulopathy. Fluid resuscitation was guided by caval index by ultrasonography, ECHO VTI and lactate level with along with the supportive therapy in the form of BiPAP. Norepinephrine was added to maintain MAP. But patient continued to have hypotensive; aggressive fluid infusion was continued till the desire parameters (Caval index, and ECHO VTI) and lactate level was attained. A total of 7 litres of crystalloid infused over 4 hrs, by the time MAP increased to 75 mmHg, urine started to come and academia correcting to near normal with lactate 3 mmol/L. Further fluid loading was done as per Caval index and ECHO VTI. Norepinephrine was gradually tapper off within 48 hours. Respiratory symptoms gradually improved over 4 days with aggressive chest physiotherapy, humidification, bronchodilator and BiPAP support. This particular case we did not had a diagnosis till a positive viral marker of epstine barr virus was obtained only after 5 days, by that time she was ready for a step down facility.

Case 3: A 46-year-obese male with medical history of psoriasis and bronchial asthma, underwent emergency surgery for diverticular perforation with primary resection and anastomosis. On 5^{th} post operative day he developed high grade fever, cough, tachypnea, tachycardia with hypotension and desaturation (SPO_2 87% on oxygen) suggestive of severe sepsis. SSC guideline was followed with aggressive fluid therapy, antibiotic, BiPAP for respiratory support as in the previous two cases.

Patient did not give consent for CVP line placement. BGA revealed PH of 7.21, PO_2 -8.4 KPa, normal PCO_2 and Lactate level was 5 mmol/L, volume status was assess initially by ECHO VTI method only, IVC was not visualized initially which might be due to presence of excessive gas in obese patients or totally collapsed IVC as visualization improved after gastric decompression and initial fluid challenge. Patient's conditions continued to fluctuate with hypotension and acidosis requiring multiple fluid challenges as judged by ECHO VTI, Caval Index and lactate reversal. After 72 hrs of ICU admission, haemodynamic stability was achieved with normal lactate level but respiratory symptoms continued to persist, CXR revealed bilateral lobar consolidation requiring BiPAP support for another 3 days before stepping down from ICU.

Case 4: A 66-year female known to have hypertension, coronary artery disease and atrial fibrillation on Warfarin 5 mg /day with past history of recurrent left ventricular failure admitted to ICU for persistent hypotension, high grade fever with cough, leukocytosis, desaturation. BGA revealed severe metabolic acidosis with Lactate 5.5 mmol/L, bilateral lung opacities on CXR suggestive of bronchopneumonia with septic shock. As patient was on anticoagulant therapy, insertion of central line was deferred. Initial resuscitation started with SSC guideline, fluid resuscitation using Caval Index and ECHO VTI, BiPAP for respiratory support. Interestingly IVC diameter was normal (2.25 cm) with no fluctuation during both phase of respiration but ECHO VTI showed low absolute value of 17 cm with 22% variation with respiration and there was progressive increase in VTI value with decrease in respiratory variability after multiple fluid challenges indicating fluid responsiveness. Norepinephrine infusion was started at a rate of 10 mcg per min to maintained MAP. After about 2 hours of fluid resuscitation with 2.5 litres of fluid, ECHO VTI value become 29 cm with less than 10% variation with respiration indicating optimum fluid balance. Despite normalization of haemodynamic parameters, lactate level remained high. Dobutamine at a rate of 5 mcg/kg/min was added to increase the cardiac output; norepinephrine infusion was gradually tapered off within 5 hrs. Dobutamine infusion continued for 48 hrs, by the time patients lactate level came to normal. BiPAP support was continued for another 24 hrs before shifting the patients to the parent ward.

Case 5: 36 year male patient met with a road traffic accident, on 5^{th} day of accident he developed a new onset abdominal pain, fever, vomiting, guarding of abdominal wall with clinical signs of breathlessness. Abdominal CT revealed a large filling defect of superior mesenteric vein diagnosed to have mesenteric venous thrombosis. CT chest revealed bilateral basal atelectasis with consolidation. He was anticoagulated with full dose heparin. Patients gradually went into sepsis with signs of septic shock with persistent hypotension, increased total count, raising lactate, low urine output. Aggressive fluid resuscitation started guided by the previous mention methods of volume estimation. Non invasive ventilation in the form of BiPAP was applied. Multiple large Fluid challenges were given based on caval index and ECHO VTI. Signs of rapid recovery were noted within 48 hours with lactate reversal and tapering of norepinephrine. Respiratory symptoms gradually improved on BiPAP support, patient was shifted to ward on 4^{th} day in stable condition.

Discussion: Surviving sepsis campaigned (SSC) guideline emphasized on early goal directed therapy (EGDT) for which placement of central venous line is invariably required, but in certain situation where central line is not available or contraindicated, the goal of EGDT can be safely achieved using non invasive techniques as reflected by our case series. We have successfully used non-invasive techniques including non-invasive ventilation and all our five patients without any complication. We did manage to keep mean arterial blood pressure of more than 65 mmHg, urine output of 0.5 ml/kg/hr.

Central line was contraindicated in four and one patient did not give consent. Fluid responsiveness is a relatively new concept, it enables the efficacy of volume expansion to be predicted before use, rather than assessed afterwards, thus avoiding inappropriate fluid infusion. Ultrasonographic IVC assessment is increasingly used for assessment of fluid responsiveness where the variation of diameter with respiration is used to determine fluid status and the response to therapy[3-6,13]. Collapsibility of superior vena cava would have been most reliable, but it requires transesophageal echocardiography[8]. Similarly, dynamic changes with passive leg raising would have been better but it was not practical in our cases as our patients were nursed in semi recumbent position.

Use of inferior vena cava (IVC) assessment and its variations with respiration is relatively new and simple method for assessing fluid volume status and the response to fluid therapy, Barbier et al used IVC diameter as a measure of fluid responsiveness in septic patients on positive pressure ventilation in a retrospective study and found that more than 18% variation in IVC diameter with respiration was strongly correlated with preload sensitivity with 90% sensitivity and 90% specificity.[4] Feissel et al also used variation of IVC diameter during respiration as a guide to fluid therapy in mechanically ventilated septic patients and found that IVC diameter variation of more than 12% allowed identification of responders with positive and negative predictive values of 93% and 92%, respectively was useful to guide fluid therapy.[5] Recently Nagdev et al[3] conducted a study to determine correlation between ultrasonographic IVC index and CVP in an emergency setting where CVP lines were inserted for resuscitation. They compared the CVP value with the caval index and found that the correlation between caval index and central venous pressure was –0.74 (95% confidence interval [CI] –0.82 to –0.63). The sensitivity of caval index greater than or equal to 50% to predict a central venous pressure less than 8 mm Hg was 91% (95% CI 71% to 99%), the specificity was 94% (95% CI 84% to 99%), the positive predictive value was 87% (95% CI 66% to 97%), and the negative predictive value was 96% (95% CI 86% to 99%)[3].

Limitation of ultrasonographic IVC assessment: Patients with increased intra-abdominal pressure the measurement of IVC diameter may not reliably correlate with the volume status and application of PEEP may overestimate the value. Technically IVC assessment may be challenging in patients with distended abdomen, ascites or obesity.

Echocardiography is a fantastic noninvasive tool which can directly visualize the heart and assess cardiac function.[10-13] ECHO VTI depends on the principle of Doppler, it measure flow in unit time across aortic valve and variation with respiratory cycle. It is a dynamic measurement and is more useful to determine the response to fluid infusion in a dynamic way. Flow dependent value like VTI will definitely be more accurate than static pressure value like CVP as per some of the recent study.[9-13] Feissel M et al in a prospective clinical trial has demonstrated that echocardiographic VTI evaluation with respiratory cycle accurately predict fluid response in septic patients on mechanical ventilation, a ΔVTI or ΔVpeak threshold value of 12% allowed discrimination between responders and nonresponders with a sensitivity of 100% and a specificity of 89%.[9] Slama et al[14] showed in an animal study that progressive blood loss was closely related to increase respiratory variation of aortic blood flow. Historically, Trans Oesophageal Echocardiograhy (TOE) has been favoured over Trans thoracic Echocardiography (TTE) in critically ill patients largely because of the challenges of obtaining images with respiration[15]. Our patients were spontaneously breathing where use of TOE was difficult to use in awake spontaneously breathing patients. Besides these parameters while assessing VTI, Cardiac contractility was also assessed by ECHO using ejection fraction method using left ventricular contractility in short axis parasternal view. This also helped in decision making of inotropic verses vasopressor agent requirement.

Limitation of ECHO VTI: ECHO VTI reflects the Cardiac Output, but it is technically more complex than ultrasonography of IVC, it may not be possible to perform in obese patients or patients with emphysematous changes. Measurements of VTI and velocity require advanced training in cardiac ultrasonography. The operator must be skilled in Doppler applications including knowledge of angle and position effect on Doppler measurements. Cardiac translation movement artefact must be recognized[16].

Now the second issue regarding tissue oxygenation, Surviving Sepsis Campaign guidelines recommend the use of central venous oxygen saturation ($ScvO_2$) or mixed venous oxygen saturation to assess the balance of tissue oxygen delivery and consumption[17]. Recently published practice surveys have indicated that the time, expertise, and specialized equipment required to measure $ScvO_2$ collectively pose a major barrier to the implementation of protocol-driven quantitative resuscitation programs.[18,19] To make it simple, many author have stressed on the use of lactate clearance calculated from two different blood sample drawn at different time which potentially represents a more accessible method to assess tissue oxygen delivery.[20,21] In a recent randomized trial by Alan E et al has shown that lactate clearance of at least 10% during early goal directed therapy for septic patients is equivalent to maintaining CVO_2 of 70% and data from this large randomized study support the substitution of lactate measurements in peripheral venous blood as a safe and efficacious alternative to a computerized spectrophotometer catheter in the resuscitation of sepsis.[22] Standard protocol as given by SSC guideline was used when lactate clearance was low. One patient in our series required infusion of dobutamine to increase cardiac output depicted by persistent low lactate clearance.

Limitations of lactate clearance: lactate level may be raised in numbers of conditions such as acute or chronic renal failure, cyanide poisoning, alcohol intoxication, mitrochondrial myopathy, liver disease, pyruvate deydrogenase or carboxylase deficiency etc and the underlying condition should be rule out before using the lactate clearance as marker of tissue oxygenation.

To improve oxygenation and avoid respiratory fatigue we applied BiPAP to all our patients it was well tolerated by all our five patients and no patient required invasive ventilation. We follow the standard principle for use of Non Invasive Ventilation such as conscious, cooperative patients, patients without active vomiting and patients with good protective airway reflexes. Non-invasive ventilation should not used for severe life threatening hypoxemia or it should be replaced by invasive ventilation if there is no improvement in respiratory parameters after 1-2 hours of initiation of BiPAP.

Standard evidence protocol was used for transfusion threshold and blood transfusion was reserved for haematocrit of 24 or less with more than 10% lactate clearance per hour. We did not transfuse any blood to any of our patient if the haematocrit was 24 or more as the lactate clearance was more than 10 to 20 percent. Even Case no 4 was despite having ischemic heart disease with haemoglobin of 8, we intent to transfuse blood, but because of unavailability of group specific blood, and lactate clearance was more than 10%, she did not received blood transfusion during the initial phase.

Conclusions: Early use of Non-invasive techniques might be more safe and productive especially during early goal directed therapy. However randomized control trial with larger sample size is definitely warranted to place these non-invasive methods as the techniques of first choice during early resuscitation phase in sepsis.

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