Low systemic vascular resistance: differential diagnosis and outcome

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Objective: To determine the frequency and prognosis of the various causes of low systemic vascular resistance (SVR).

Design: Analysis of consecutive patients over a 5-year period; retrospective review.

Setting: Medical intensive care unit of a large university hospital.

Patients: Fifty-five patients with unexplained hypotension and a SVR less than 800 dynes × s/cm^5.

Background: There are minimal data in the medical literature determining the frequency or outcome of patients with a low SVR that is unrelated to sepsis or the sepsis syndrome. We retrospectively reviewed and analyzed all hemodynamic data in a large university hospital over a 5-year period to determine the frequency and prognosis of the various causes of low SVR. Fifty-five patients with unexplained hypotension and a SVR less than 800 dynes × s/cm^5 were identified.

Main results: Twenty-two patients (Groups 1 and 2) met the criteria for sepsis syndrome. The mean SVR for this group was 445 ± 168 dynes × s/cm^5 with an associated mortality of 50%. Group 3 contained 20 patients with possible sepsis. Thirteen patients (Group 4) were nonseptic. The mean SVR of this group was 435 ± 180 dynes × s/cm^5 with an associated mortality of 46%. Extremely low SVR (below 450 dynes × s/cm^5) was associated with a significantly higher mortality regardless of the etiology.

Conclusions: At least a quarter of patients with hypotension and a low SVR have nonseptic etiologies. The patients with nonseptic etiologies have a similar mortality to septic patients. Clinicians should be aware of the wide spectrum of conditions that induce a low SVR.

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Keywords: systemic vascular resistance, hypotension, sepsis, cirrhosis, pancreatitis, adrenal insufficiency, anaphylaxis

Received: 11 January 1999
Revisions requested: 30 March 1999
Revisions received: 10 May 1999
Accepted: 11 May 1999
Published: 9 June 1999

Crit Care 1999, **3**:71–77

The original version of this paper is the electronic version which can be seen on the Internet (http://ccforum.com). The electronic version may contain additional information to that appearing in the paper version.

Introduction

As initially described by Poiseuille's law, resistance to flow is that resistance provided by a vessel or circulatory bed which permits a given pressure differential to produce a unit flow. Transcribed to human hemodynamics, systemic vascular resistance (SVR) can be measured from the differential pressure between the mean arterial pressure (MAP) and the central venous pressure (CVP) divided by the flow, ie cardiac output (CO). Although many clinical conditions can cause a low SVR, septic shock remains the most common cause and usually results in a severe decrease in SVR. In more than 90% of patients with septic shock who are aggressively volume loaded, the CO is initially normal or elevated. Therefore, hypotension results from reduced vascular resistance with normal or elevated CO. This form of shock results from maldistribution of blood flow to tissues, usually from acute vasodilatation without concomitant expansion of the intravascular volume. While distributive shock can also be caused by anaphylaxis, drug ingestion, neurogenic injury, and adrenal insufficiency, these conditions are seen with less frequency in the intensive care unit. Therefore, a hemo-

SVR = systemic vascular resistance; MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output; CI = cardiac index; SVRI = systemic vascular resistance index; WBC = white blood count; EHS = extreme hyperdynamic state; TNF = tumor necrosis factor; IL = interleukin; ACTH = adrenocorticotrophic hormone; ATP = adenosine triphosphate.

dynamic state with low SVR is often considered synonymous of sepsis, and other conditions associated with a low SVR may not be considered.

There are minimal data in the medical literature assessing the frequency or outcome of patients with distributive shock that is unrelated to sepsis or the sepsis syndrome. Since we could find no prior studies in the literature assessing the etiology and outcome of hypotensive patients with a low SVR, we reviewed our experience with patients undergoing hemodynamic monitoring in the medical intensive care unit of a large university hospital. The purpose of this study was to determine the different causes of low SVR, identify prognostic factors, and analyze the mortality of these various groups of patients.

Methods

After approval by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, medical records of all patients admitted to the medical intensive care unit of the University Hospital between 1990–1995 were reviewed. All the charts of patients undergoing pulmonary artery catheterization were identified. Patients with a recorded SVR less than 800 dynes × s/cm^5 were analyzed. The main indication for pulmonary artery catheterization in patients in this study was unexplained hypotension after volume challenge. Any patient with an unclear etiology for hypotension or any patient requiring more than 10 μg/kg/min dopamine underwent pulmonary artery catheterization and was reviewed for this study. Anxiolytics, sedatives, and neuromuscular blocking agents are administered by protocol and have minimal or no direct effects on hemodynamics or histamine release. Cultures of blood and urine were obtained on all patients; cultures of sputum, pleural fluid, ascitic fluid, and cerebrospinal fluid were obtained as clinically indicated. Toxicological screening of blood and urine for drugs was performed on admission if the etiology of hypotension was in question. Serum cortisol level determination was performed on all patients receiving exogenous corticosteroids or in patients with known risk factors for adrenal insufficiency. Hematologic and blood chemistry determinations, arterial blood gases, routine urinalysis, and serial electrocardiograms were obtained on all patients.

Mean systemic, right atrial, and pulmonary artery pressures and thermodilution cardiac outputs were measured every 4 h in all patients. Derived hemodynamic variables were calculated as follows: cardiac index (CI; l/min/m^2) = CO/body surface area; SVR (dynes × s/cm^5) = (80 × MAP)/CO; and systemic vascular resistance index (SVRI) = SVR/body surface area. Patients received vasopressors to maintain MAP above 70 mmHg. The set of hemodynamic data with the lowest SVR was selected for each patient.

All historical, clinical, laboratory, microbiologic, and hemodynamic data were studied. Patients were divided into four groups based on the following parameters: (1) positive blood culture; (2) temperature ≥38.1°C or ≤36°C; (3) white blood counts (WBCs) ≥12 000/mm^3 or ≤4000/mm^3; and (4) obvious source of infection. Group 1 (definite sepsis) had positive blood cultures and two or more criteria; Group 2 (probable sepsis) had an obvious source of infection and two or more additional criteria; Group 3 (possible sepsis) had fever and leukocytosis or leukopenia with no obvious source of infection nor positive blood culture; and Group 4 (nonseptic) had none of the criteria.

The clinical course, laboratory findings, hemodynamics, and intensive care unit mortality were compared between the various groups. Data are expressed as mean ± standard deviation. Clinical and hemodynamic variables were compared with a student's *t*-test and by analysis of variance to assess statistical significance between groups. Logistic regression analysis was performed comparing SVR and death using a univariant analysis.

Mortality was assessed by Mann-Whitney rank sum test. A P value of ≤0.05 was considered statistically significant.

Results

Fifty-five patients were included in the study (Table 1). Group 1 contained 18 patients with definite sepsis; Group 2 contained four patients with probable sepsis; Group 3 contained 20 patients with possible sepsis; and Group 4 contained 13 patients who had no evidence of sepsis. The mean age of the patients was 50 ± 13.6 years. Thirty-four patients were men, and 21 patients were women. The overall MAP was 72 ± 20 mmHg at the moment the hemodynamic values were chosen. The overall mean CO was 9.2 ± 6.18 l/min, and the mean CI was 5.1 ± 1.7 l/min/m^2. The overall mean SVR was 435 ± 180 dynes × s/cm^5; the mean SVRI was 785 ± 325 dynes × s/cm^5. Analysis of SVRI was reviewed for each subgroup and not found to be different from the analysis of SVR; therefore, only data for SVR are presented.

There were no statistically significant differences in age, sex, or admission temperature among the different groups. Twenty-two patients (Groups 1 and 2) met the criteria for the sepsis syndrome [1]. The mean SVR was 445 ± 168 dynes × s/cm^5, CO was 10.86 ± 5.22 l/min; and CI was 5.08 ± 1.64 l/min/m^2 for this group. The overall mortality in those patients classified as having the sepsis syndrome was 50%. In patients with the sepsis syndrome, the lung was the primary site of infection in 14 out of 22 patients. Thirteen patients were considered nonseptic (Group 4). This group had no source of infection, alteration in temperature, leukocytosis, or leukopenia. The mean hemodynamic values for this group were: SVR = 435 ± 180 dynes × s/cm^5; CO = 9.23 ± 4.24 l/min, and CI = 7.72 ± 1.9 l/min/m^2. The mortality was 46%. There

Table 1

Clinical parameters of study groups

Group	Number	Age[a] (mean ± SD)	Temperature[b] (mean ± SD)	Clinical diagnoses
Group 1: definitive sepsis	18	52 ± 12	101.5 ± 1.6°F	Pneumonia (10); urinary tract infection (3); abdominal sepsis (2); toxic shock syndrome (1); meningitis (1); cellulitis (1)
Group 2: probable sepsis	4	48 ± 10	99.3 ± 4.17°F	Pneumonia (4)
Group 3: possible sepsis	20	51 ± 12.5	100.3 ± 2.36°F	Spontaneous bacterial peritonitis (5); idiopathic (3)
Group 4: nonseptic	13	44 ± 17	98.4 ± 1.8°F	Cirrhosis (5); idiopathic (4); pancreatitis (3); adrenal insufficiency (1)

[a]$P > 0.05$; [b]$P < 0.01$, between Group 1 + 2 versus Group 4

Table 2

Mean hemodynamic values and mortality (± SD)[a]

Group	Number	MAP	CO	CI	SVR	Mortality
Group 1: definitive sepsis	18	67.6 ± 22.7	10.19 ± 3.3	5.23 ± 1.5	455 ± 144	8/18 (44%)
Group 2: probable sepsis	4	50.0 ± 27.6	9.83 ± 3.6	4.38 ± 1.9	506 ± 123	3/4 (75%)
Group 3: possible sepsis	20	71.4 ± 15	9.70 ± 3.0	5.37 ± 1.6	483 ± 167	12/20 (60%)
Group 4: nonseptic	13	74.7 ± 29	9.23 ± 4.2	4.72 ± 1.9	507 ± 222	6/13 (46%)
Combined data	55	71.7 ± 20.8	9.76 ± 0.36	5.10 ± 1.7	435 ± 180	29/55 (53%)

MAP, mean arterial pressure (mmHg); CO, cardiac output (l/min); CI, cardiac index (l/min/m^2); SVR, systemic vascular resistance (dynes × s/cm^5). [a]$P > 0.05$ for comparisons for hemodynamics and mortality between groups.

were no statistically significant differences in any hemodynamic values nor in mortality between the nonseptic group (Group 4) and the groups with sepsis syndrome (Groups 1 and 2). The nonseptic group included eight patients with intra-abdominal disease (five with decompensated cirrhosis, three with acute pancreatitis), one patient with adrenal insufficiency, and four patients with unclear etiologies for hypotension and low SVR (idiopathic). The mortality in patients with decompensated intra-abdominal disease was 75% (six out of eight). Additionally, no statistically significant difference in any of the hemodynamic values or mortality was identified between the four groups when analyzed individually (Table 2).

Twenty-seven patients met the criteria for the extreme hyperdynamic state (EHS). In the literature [2], EHS is defined as an SVR below 450 dynes × s/cm^5 and a CO above 7 l/min/m^2. The mean hemodynamic values for patients in this study with EHS were: SVR = 327 ± 85 dynes × s/cm^5; CO = 12.13 ± 3.31 l/min; and CI = 5.98 ± 1.46 l/min/m^2. Seven of these patients had a diagnosis of underlying cirrhosis. Twelve of the patients within this group were diagnosed with sepsis syndrome, 10 with possible sepsis, and five were nonseptic. This group had a statistically significant higher mortality (60% versus 33%) than those patient without the EHS ($P < 0.05$). A univariant logistic regression was performed analyzing the level of reduction of SVR and mortality. A statistically significant relationship was found between these variables ($P = 0.025$). For every reduction in SVR of 50 dynes × s/cm^5, there was a 20% increase in mortality (odds ratio = 1.2; range = 1.022–1.434).

Discussion

Sepsis and sepsis syndrome were the most common etiologies of a low SVR in this study. Although many studies have found urinary or intra-abdominal sepsis to be the most common cause of low SVR [3], the lung was the primary site of infection in over half of our patients.

Septic shock, the leading cause of intensive care unit mortality, is caused by systemic activation of the inflammatory cascade. Numerous mediators, including cytokines, kinins, complement, coagulation factors, and eicosanoids, are activated or systematically released, resulting in profound disturbances of cardiovascular and organ system function. These mediators, particularly tumor necrosis factor (TNF), interleukin (IL)-1, platelet activating factor, and prostaglandins, are thought to mediate the reduced peripheral vascular resistance seen in septic shock [4–6].

Parker *et al* [7] studied serial cardiovascular variables in humans with septic shock. A low SVR was seen in both survivors and nonsurvivors; however, persistently low SVR beyond 24 h was a strong predictor of mortality. This study demonstrated that the majority of patients (65%) who die of septic shock have a persistently low SVR, while a smaller percentage die of low CO (10%) or of multiple organ failure (25%) after hemodynamic resolution of shock. Although we did not evaluate serial hemodynamic profiles in this study, our data identify a group of patients with EHS who demonstrate a SVR below 450 dynes × s/cm^5 and a mean CO over 12 l/min. As with patients in prior studies [2], this group demonstrated a significantly higher mortality. Although the mechanisms relating to the difference in mortality are unknown, it has been suggested that patients with "complicated" shock (defined as multiorgan failure) have greater distortions of cardiorespiratory patterns relative to the degree of hypotension and that this is associated with a higher mortality [8,9]

Our study demonstrates that patients with sepsis syndrome are the most common group of patients presenting with hypotension and a low SVR in the medical intensive care unit. This group only represents approximately 40% of patients in our study. While many of the remaining patients had some evidence supporting the diagnosis of sepsis (eg fever, leukocytosis), they lacked an identifiable source of infection, and the exact etiology of their hypotension remains unknown. More significantly, almost one-quarter of the patients (24%) in this study developed hypotension and a low SVR without any evidence of sepsis. This group had a high mortality (46%), similar to the remaining patients (54%). There were no significant differences in the clinical or hemodynamic parameters between the nonseptic patients and the patients in the remaining groups. The frequency of nonseptic causes of a low SVR suggest that clinicians must be aware of conditions other than sepsis that have either been well documented (Table 3) or reported to induce a reduction in the SVR (Table 4).

The largest group of nonseptic patients in this study with hypotension and a low SVR was found to be patients with decompensated cirrhosis. Although occult infections should not be excluded, none of these patients had fever, leukocytosis, an identifiable site of infection, or abnormalities in the peritoneal fluid. Patients with liver cirrhosis often present with systemic hemodynamic disturbances, including hypotension, low SVR, and a reduced sensitivity to vasoconstrictors [10]. The precise mechanisms of these hemodynamic disorders have not yet been clearly elucidated. Excessive production of vasodilators, peripheral shunts, and increased levels of nitric oxide in these patients may contribute to the hyperdynamic state observed in this population [10–16]. A recent study by Matsumoto [16] demonstrated that patients with decompensated liver cirrhosis had higher levels of exhaled nitric oxide than patients with compensated cirrhosis, chronic liver disease, or controls. The decompensated cirrhotics had a significantly higher CO and a lower SVR than the compensated patients. Additionally, a positive correlation was found between the level of nitric oxide and CI. Five of our patients with a low SVR had decompensated liver disease as the presumed etiology of their hypotension. Another five patients in the possible sepsis group had hypotension with a clinical diagnosis of spontaneous bac-

Table 3

Documented conditions associated with low SVR

Condition	Comment
Sepsis	Most common cause of low SVR
Pancreatitis	Seen with necrotizing or hemorrhagic pancreatitis
Cirrhosis	Seen with decompensated liver disease
Adrenal insufficiency	Only 15 well documented cases
Head injury	Seen after initial rise in SVR
Beriberi	Rapid response to thiamine
Salicylate (chronic)	Seen in elderly patients, illness mimics sepsis
TMP-SMX	Reported only in AIDS patients
Vasoplegic syndrome	Occurs within 6 h postcardiopulmonary bypass Incidence estimated to be 0.4%–5.0%

SVR, systemic vascular resistance (dynes × s/cm^5); TMP-SMX, trimethoprim-sulfamethoxazole. See text for discussion.

Table 4

Conditions reported to have low SVR

Condition	Comment
Anaphylaxis	Conflicting hemodynamic data; low SVR after fluid repletion
Myocardial infarction	Rare, minimal evidence in humans
Ovarian hyperstimulation syndrome/burns	Hyperadrenergic and hypermetabolic state
Thyrotoxicosis	Animal studies only
Multiple myeloma	Three documented cases
Anemia	Hemoglobin < 7 g; results not reproducible
Hyperthermia	Few well-documented cases
Tricyclic antidepressants	Little hemodynamic data available
Paget's disease	Arterovenous shunts
Spinal cord injury	Injury above T6; inhibited vagal tone

SVR, systemic vascular resistance in dynes × s/cm^5

terial peritonitis; however, the lack of positive cultures, or any other evidence of infection, suggest that decompensated liver disease may have played a significant role in their hypotension.

Pancreatitis was found to be the second most common cause of low SVR in patients without evidence of infection. Three patients had necrotizing pancreatitis, with one of these having evidence of hemorrhage into the pancreas. Hemodynamic manifestations of pancreatitis include a normodynamic or hypodynamic state, usually present in acute interstitial pancreatitis and commonly associated with hypovolemia. Pancreatitis can also present as a hyperdynamic state with high CO and a low SVR as described by Di Carlo *et al* [17] and Bradley *et al* [18]. This hyperdynamic state is another manifestation of the severity of acute pancreatitis and is seen mostly in necrotizing pancreatitis with or without hemorrhage [19]. Severe pancreatitis may mimic sepsis syndrome or septic shock despite the absence of any infectious site. The mechanisms responsible for pancreatic shock have not been elucidated; however, an inflammatory cascade generalized by cytokines and TNF is felt to be the most likely cause of this process [17–19].

Adrenal insufficiency was found in one of our patients with no evidence of infection. Unfortunately, cortisol levels and adrenocorticotrophic hormone (ACTH) response was not routinely measured in patients with infection, and adrenal insufficiency may have been underestimated in this group. Adrenal insufficiency may present as a hypodynamic, normodynamic, or hyperdynamic state [20]. The hypodynamic state is usually seen early in adrenal insufficiency and is associated with volume depletion from diarrhea, vomiting, and decreased reabsorption of sodium in the distal tubule. CO may also be decreased in adrenal insufficiency as the result of the myofibrillar adenosine triphosphate (ATP) depletion seen with glucocorticoid deficiency [20]. Intravenous fluid therapy most often increases CO and decreases SVR in patients with adrenal crisis. These patients are usually separated from patients with sepsis by a baseline cortisol level below 10 μg/dl or an inadequate response to ACTH [20]. One of our patients with septic shock had baseline cortisol of 22 μg/dl and no response to the cosyntropin stimulation test. This patient could not be weaned off high dose norepinephrine and dopamine until intravenous corticosteroids were instituted. Normal values for basal and stimulated cortisol levels are derived from the adrenal response of healthy individuals. Patients experiencing the severe stress of critical illness demonstrate higher than normal amounts of circulating cortisol. Some patients with critical illness have minimal or no ACTH stimulation above their baseline cortisol levels and may be unable to respond to additional physiologic stress [20]. Several reports suggest a significant number of critically ill patients may have unrecognized adrenal insufficiency [21–24].

Four cases of idiopathic hypotension with low SVR were identified in our patients. One case was felt to be related to possible anaphylaxis or anaphylactoid reaction but was not well documented. Silverman *et al* [25] reported a patient who developed anaphylactic shock secondary to penicillin 7 days postmyocardial infarction; the hemodynamic parameters showed a decrease in CO and MAP with an increase in SVR. Moss *et al* [26] reported the opposite hemodynamic profile in a patient with anaphylactic shock secondary to succinycholine. Their patient developed a low SVR and a high CO which correlated with increased levels of histamine and catecholamines. Although there are minimal human data, animal studies suggest there is an initial hypodynamic state secondary to severe extravasation of fluids into the tissues followed by a hyperdynamic state after fluid resuscitation.

Our second case of hypotension with a low SVR presented in the setting of an acute myocardial infarction. Although cardiogenic shock presents with a high SVR and low CO, some data suggest that, rarely, patients may present with a syndrome of low SVR. McCriskin *et al* [27] reported a patient with a left ventricular pseudoaneurysm postmyocardial infarct with a low SVR and no evidence of infection. Costantin [28] developed an animal model in dogs and demonstrated a subset of animals with a hyperdynamic state after coronary occlusion; however, Ross *et al* [29] were unable to confirm these results using another animal model. Similarly, Smith *et al* [30], in one of the original hemodynamic descriptions of patients after myocardial infarction, did not identify any patient with a hyperdynamic state. Another recently described cause of low SVR in cardiac patients is the "vasoplegic syndrome". This syndrome occurs within 6 h after cardiac surgery using extracorporeal circulation [31]. The incidence has been estimated between 0.4 and 5% of patients undergoing cardiovascular surgery using cardiopulmonary bypass [31,32]. The etiology is unclear but has not been associated with increased levels of nitric oxide or endotoxin.

One patient with a low SVR classified as idiopathic had a history of significant alcohol consumption. Their initial hemodynamic parameters showed a low SVR with high CO which rapidly resolved after intravenous thiamine and broad-spectrum antibiotics. It is possible that this case represents a variant of beriberi heart disease. This rare but treatable disease should be considered in every patient with congestive heart failure and a low SVR. The fulminant form known as Shosin beriberi presents as a high CO state with extremely high CO and a low SVR which rapidly responds to thiamine [33–35].

The remaining patient in the idiopathic group had no explanation for their low SVR syndrome. Review of the literature shows many causes of a low SVR (Tables 3 and 4), and it is possible that one of these diagnosis was missed

by the clinicians caring for this patient. The patient had normal urine drug abuse screens and a normal serum acetaminophen level. A salicylate level was not obtained. Leatherman and Schmitz [36] reported a series of five patients who became accidentally intoxicated with salicylates with clinical, laboratory, and hemodynamic features of sepsis, but without bacteriological evidence. In two of the cases, TNF-α, IL-1 and IL-6 were measured and found to be significantly elevated. Other drugs have been associated with a low SVR including tricyclic antidepressants, anesthetic agents, and narcotics. Recently Nguyen *et al* [37] reported hyperdynamic shock caused by trimethoprim-sulfamethoxazole in which immunoglobulin E antibodies and TNF were not detected and complement levels were normal, suggesting a mechanism other than anaphylaxis. Our drug screen should have identified tricyclic antidepressants or narcotics in the urine; however, a careful drug history was not elicited in this patient. Although other conditions such as head injury [38–40], Paget's disease [41–43], arteriovenous fistula [44], severe anemia [45,46], multiple myeloma [47], thyrotoxicosis [48], and spinal cord injury [49] have been reported to produce a low SVR, this patient lacked any clinical evidence suggesting one of these diagnoses; his hypotension resolved spontaneously.

Conclusion

In summary, we describe a group of 55 patients with a SVR below 800 dynes × s/cm^5, and a subgroup of 13 non-septic patents (24%) with a similar mortality. This study emphasizes the importance of considering other conditions besides sepsis in patients presenting with hypotension and a low SVR.

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